AN INVESTIGATION OF *N*-BENZYL AMIDE SYNTHESIS *VIA* OXYPYRIDINIUM SALTS

A THESIS

SUBMITTED TO THE GRADUATE SCHOOL

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BY

MARYAM BANIASAD

DR. PHILIP ALBINIAK – ADVISOR

BALL STATE UNIVERSITY

MUNCIE, INDIANA

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Table of Contents

Chapter 1: Background and Introduction

Chapter 2: Synthesis of *N*-Benzyl Amides

Appendix: Supporting Information regarding *N*-Benzyl Amide Synthesis

List of Schemes

Chapter 1

List of Figures

Chapter 1

Chapter 2

List of Tables

Chapter 1

Chapter 2

List of Abbreviations

Salts:

BnOLT: 2-Benzyloxy-1-methyllepidinium triflate

BnOPT: 2-Benzyloxy-1-methylpyridinium triflate

Solvents:

DMF: Dimethylformamide

$PhCF_3$: Trifluorotoluene

THF: Tetrahydrofuran

Reagent:

MeOTf: Methyl triflate

PMBO-lepidine: *p*ara-methoxybenzyloxy lepidine

Bases:

Et_3N: Triethylamine

MgO: Magnesium Oxide

NaOH: Sodium Hydroxide

SDS: Sodium Dodecyl Sulfate

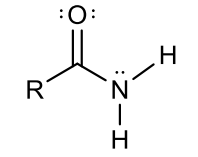
TEA: Triethylamine

CHAPTER 1: BACKGROUND AND INTRODUCTION

1.1 Amides

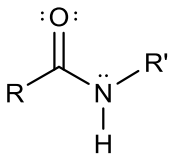
The term amide refers to a class of chemical compounds with a functional group that consists of a carbonyl group bonded to a nitrogen from one side and a carbon on the other side. Amides are regarded as derivatives of carboxylic acids in which the -OH of the acid has been replaced by -NR_2 where R= H, alkyl, aryl. Like amines, amides can be classified as "primary", "secondary" or "tertiary" depending on the degree of carbon substitution on nitrogen[1]**(Scheme 1.1)**.

Scheme 1.1: Three Classes of Amides



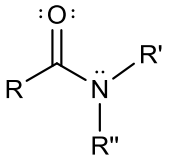
Primary Amide

(1.1)



Secondary Amide

(1.2)

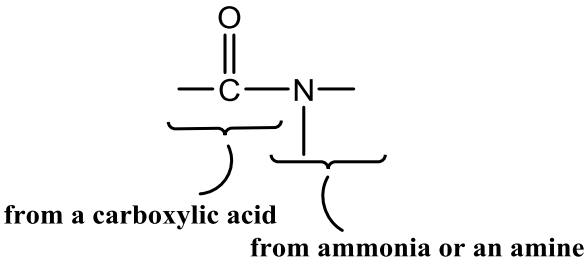


Tertiary Amide

(1.3)

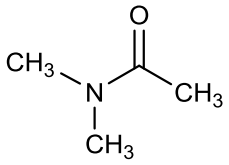
The simplest amides are derivatives of ammonia in which one hydrogen atom has been replaced by an acyl group. The ensemble is generally represented as $RC(O)NH_2$ and is described as a primary amide **(1.1)**. Closely related and even more numerous are secondary amides **(1.2)** which can be derived from primary amines ($R'NH_2$) and have the formula RC(O)NHR′. Tertiary amides **(1.3)** are commonly derived from secondary amines (R′R″NH) and have the general structure RC(O)NR'R". The amide functionality is also regarded as derivative of carboxylic acids in which the hydroxyl group has been replaced by an ammonia or amine[1]**(Scheme 1.2)**.

Scheme 1.2: Amide Functional Group



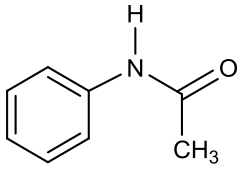
Amides may also be sub-classified as aliphatic, aromatic (i.e. anilides or benzamides) or cyclic (lactams), based on the nature of the nitrogen substituents and overall structure. Aliphatic amides **(1.4)** have simple hydrocarbon substituents (alkyl groups) while aromatic amides **(1.5)** have at least one aromatic ring substituent as shown in the example below. Lactams **(1.6)** contain an amide group as part of a cyclic structure **(Scheme 1.3)**.

Scheme 1.3: Aliphatic and Aromatic Amides



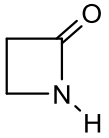
Tertiary Aliphatic Amide

(1.4)



Aromatic Amide

(1.5)



Lactam (Cyclic Amide)

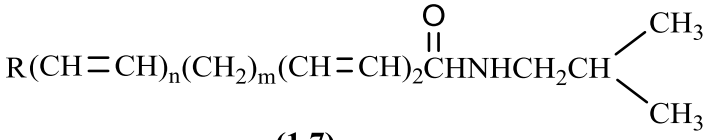
(1.6)

1.2 Applications of Amides

An amide group is found in many natural and synthetic materials, and its derivatives are applied in various pharmaceutical and biochemical fields. Amides are also widespread in compounds with a broad range of applications in biotechnology, agriculture, industry and medicine.[2] For example, in agriculture, in 1981 three amides were isolated from black pepper, *Piper nigrum* L, and identified from their NMR and MS spectral data as *N*-(2-methylpropyl)-2,4-decadienamide **(1.7a)**, 13-(1,3-benzodioxol-5-yl)-*N*(2-methylpropyl)-2,4,12-tridecatrienamide **(1.7b)**, and 11-(1,3-benzodioxol-5-yl)-*N*-(2-methylpropyl)-2,4,10-undecatrienamide **(1.7c)**.[3]

These compounds have been reported to have biological activity on insects as toxins. Therefore, they could be used as pesticides for preventing, destroying, repelling or mitigating any pest.[3]

Scheme 1.4: Amides Isolated from *Piper nigrum*[3]



(1.7)

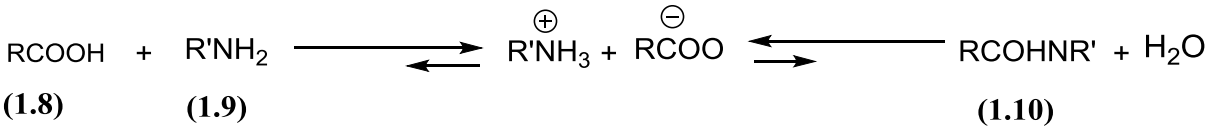
(1.7)	n	m	Empirical formula
a	0	3	$C_{14}H_{25}NO$
b	1	6	$C_{24}H_{33}NO_3$
c	1	4	$C_{22}H_{29}NO_3$

In industry, amides are commonly used as solvents with specific properties. Dimethylformamide, commonly abbreviated as DMF, is a colorless liquid miscible with water and the majority of organic liquids.[4] DMF is commonly used as a solvent due to its low evaporation rate. DMF is also used in the production of acrylic fibers and plastics.[4] It is also used as a solvent in peptide coupling for pharmaceuticals[5], in the development and production of pesticides,[3] and in the manufacture of adhesives, synthetic leathers, fibers, films, and surface coatings.[4] In medicine, amides are important functional group present in a number of drugs molecules (local anesthetics, antiarrhythmics, and antiviral).[6,7]An in-depth analysis of the comprehensive medicinal chemistry database revealed that the amide group appears in more than 25% of known drugs.[2] The amide functionality is also the key linking moiety in proteins and peptide drug products.[7] Therefore, it is ubiquitous in life, as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen).[2]

1.3 Synthesis of Amides

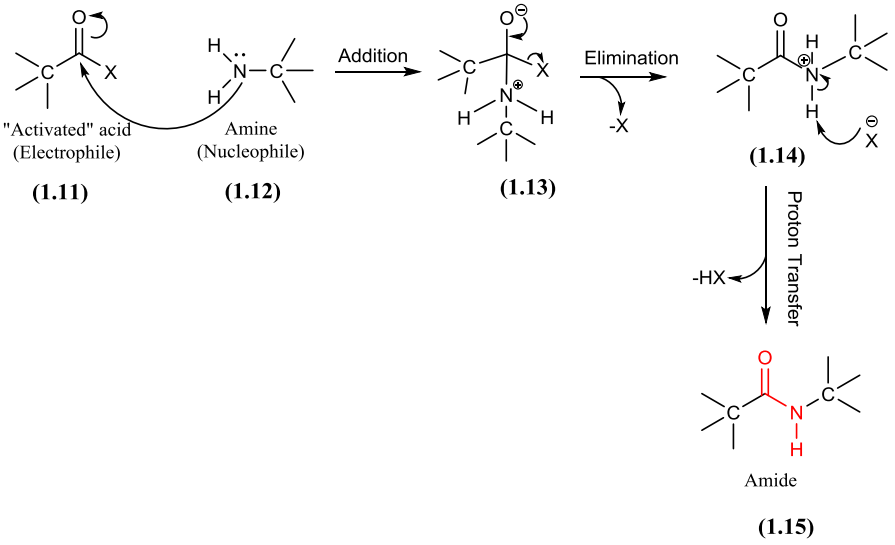
The synthesis of amides is of huge importance in a wide variety of industrial areas and is of particular significance in the synthesis of pharmaceuticals. In theory, the simplest method for making amides is by coupling a carboxylic acid with an amine. However, this reaction is not the most efficient way of producing amides. The Amide bond formation between a carboxylic acid **(1.8)** and an amine **(1.9)** is formally an acid-base reaction, which means on mixing an amine with a carboxylic acid, an acid-base reaction occurs first to form a stable salt. In other words, the amide bond formation has to fight against adverse thermodynamics as the equilibrium shown in **Scheme 1.5**.

Scheme 1.5: Amide Bond Formation



Therefore, with competing products, the nucleophilic acyl substitution reaction between the two is not the most effective way to isolate an amide **(1.10)**. A better procedure would be the reaction between an activated carboxylic acid derivative **(1.8)**, and an amine **(1.9)**. In fact, by activating carboxylic acid, a better leaving group is attached to the acyl carbon of the acid and provides better chance of nucleophilic attack from the nitrogen of amine group **(Scheme 1.6)**.[2]

Scheme 1.6: Basic Method of Amide Synthesis Using Activated Acid

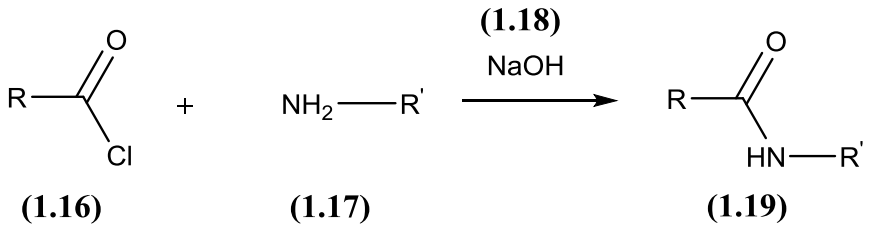


As shown in **Scheme 1.6**, an activated carboxylic acid **(1.11)** is achieved by first converting carboxylic acid to a better electrophile like an acyl halide, which is a key idea in the Schotten-Baumann reaction pathway.

1.3.1 Schotten–Baumann Reaction

An acyl halide **(1.16)** is a reactive molecule that is formed by replacement of the hydroxyl group in the carboxylic acid with a halide.[8] The halide replacement can activate the addition step in reaction of carboxylic acid and amine by making the acyl carbon of the acid more electrophilic through either the electronegativity or polarizability. Additionally, elimination step would be more activated in presence of a halide by providing a better leaving group and by losing the acidic hydrogen. With an electrophilic carbon present in the structure of activated carboxylic acid, the nucleophilic nitrogen of the amine **(1.17)** will easily react with the acyl halide **(1.16)** to form an amide **(1.19)**. This method is called Schotten–Baumann reaction[9] **(Scheme 1.7)**.

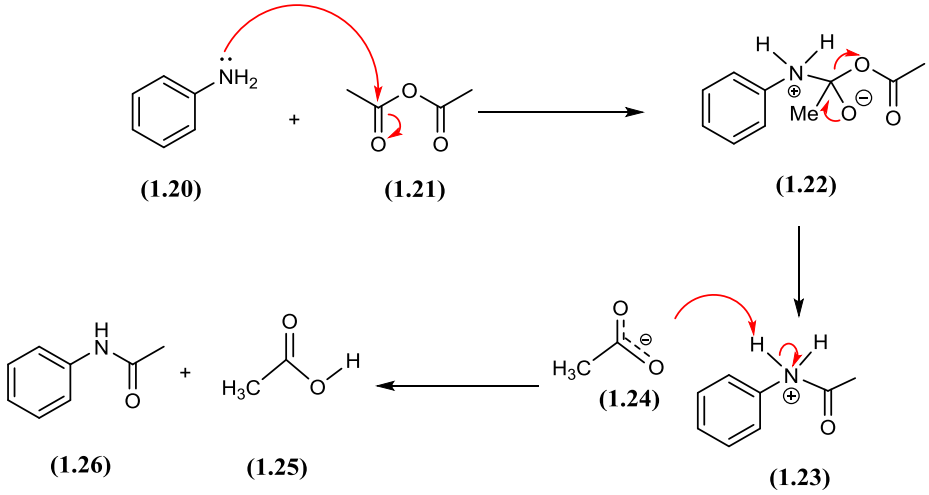
Scheme 1.7: Schotten–Baumann Reaction Scheme



1.3.2 Lumière–Barbier Reaction

The conversion of carboxylic acid to an anhydride would also prepare an activated carboxylic acid derivative **(1.21)** for amide synthesis. The reaction of aromatic amine **(1.20)** with an anhydride **(1.21)** is a method of acetylating aromatic amines in aqueous solutions **(Scheme 1.8)**.[10]

Scheme 1.8: Lumière–Barbier Reaction Scheme

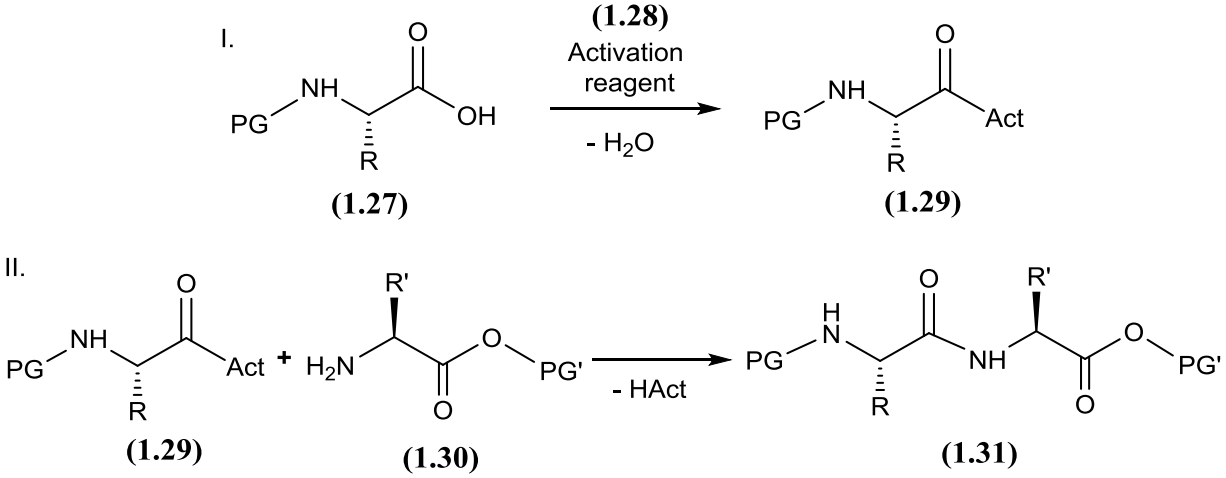


1.3.3 Peptide Coupling Reaction

A coupling reaction results in the formation of an amide bond between amino acids and/or peptides which plays a crucial step in peptide synthesis.[2] The reaction consists of two consecutive parts: 1) activation of the carboxyl moiety, and 2) acylation of the amino group **(Scheme 1.9)**.

Amide bond formation can often present difficulties such as low yields, racemization at α-stereocenter, formation of undesirable byproducts, and difficult purification.[2] To face these challenges, numerous mild coupling reagents and methods have been developed that not only are high yielding, but also potentially prevent racemization of neighbouring chiral centres.[11] As shown in **Scheme 1.9** during the first step the protected amino acid **(1.27)** (or peptide) reacts with a coupling reagent **(1.28)** yielding a reactive intermediate **(1.29)**. In the second step, the intermediate **(1.29)** is attacked by a nucleophile such as the α-amino group of a carboxy-protected amino acid **(1.30)**. In the past two decades, different types of coupling reagents have been designed to be used in step one of this reaction which is a crucial step in peptide bond formation.[2] Today, further investigation has been tried for the synthesis of new coupling reagents. Many of these reagents have been developed to enable the coupling of specific amino acids, or to work in conjunction with a precise protecting group (e.g., Fmoc, and Boc).[2]

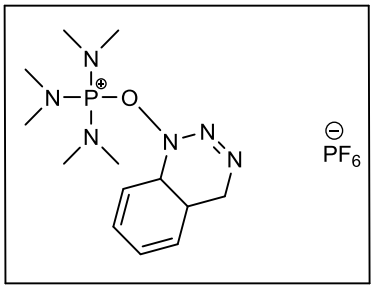
Scheme 1.9: Activation and coupling of a protected amino acid. PG: protecting groups. Act: activating group[11]



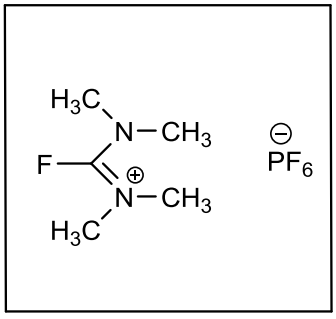
A significant number of the coupling reagents like carbodiimides are commercially available. Carbodiimides have been used as activators for decades in solid-phase and solution peptide

synthesis. DCC (Dicyclohexylcarbodiimide) is one of the popular carbodiimides which has been applied for coupling since 1955 and is still much in use today.[11] In recent years two classes of coupling reagents became more popular, the phosphonium type reagents such as (benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate (BOP) **(1.32)**,[12] (benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate (PyBOP)[12], and bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP)[13], and the aminium type reagents like tetramethylfluoroformamidinium hexafluorophosphate (TFFH) **(1.33)**,[14] (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) **(Scheme 1.10).**[2,11] These compounds achieve high coupling rates accompanied by few undesired side reactions. In contrast to activation by carbodiimides, peptide couplings using the latter compounds require the presence of a base.

Scheme 1.10: Phosphonium (BOP) and Imonium (TFFH) Coupling Reagents[11]



(1.32)



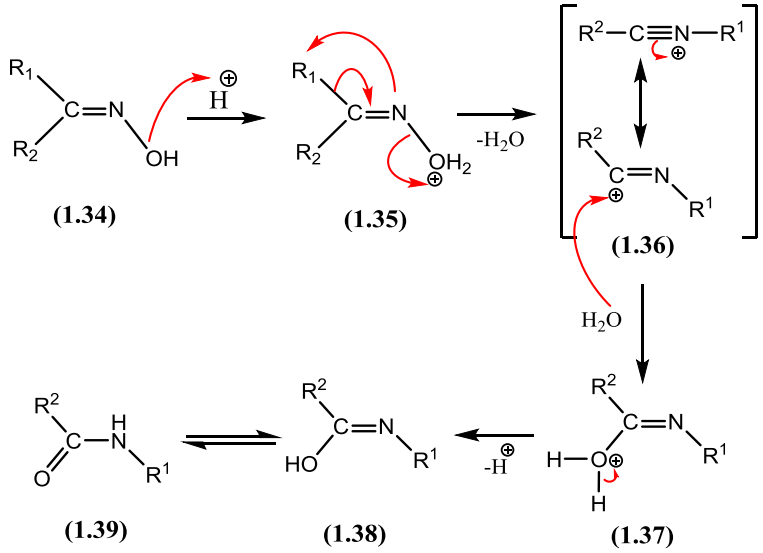
(1.33)

1.3.4 Beckmann Rearrangement

The Beckmann rearrangement is an alternative method of amide synthesis. The Beckmann rearrangement involves formation of oximes **(1.34)** (from the reaction of aldehydes or ketones with hydroxylamine) and a subsequent acid-catalyzed rearrangement of that oxime to an amide **(1.39)** or nitriles. Oximes **(1.34)** derived from ketones form amides **(1.39)**; oximes derived from aldehydes form nitriles).[15] This is generally achieved through conversion of the oxime oxygen to a good

leaving group by protonation, followed by heat, which results in an alkyl (or hydride) shift, breaking the weak N-O bond. The second step involves trapping of the electrophilic carbon in **(1.36)** with water (forming an amide) or, if a hydride shift occurred, deprotonation of nitrogen to give a nitrile **(Scheme 1.11)**

Scheme 1.11: Beckmann rearrangement Reaction Scheme

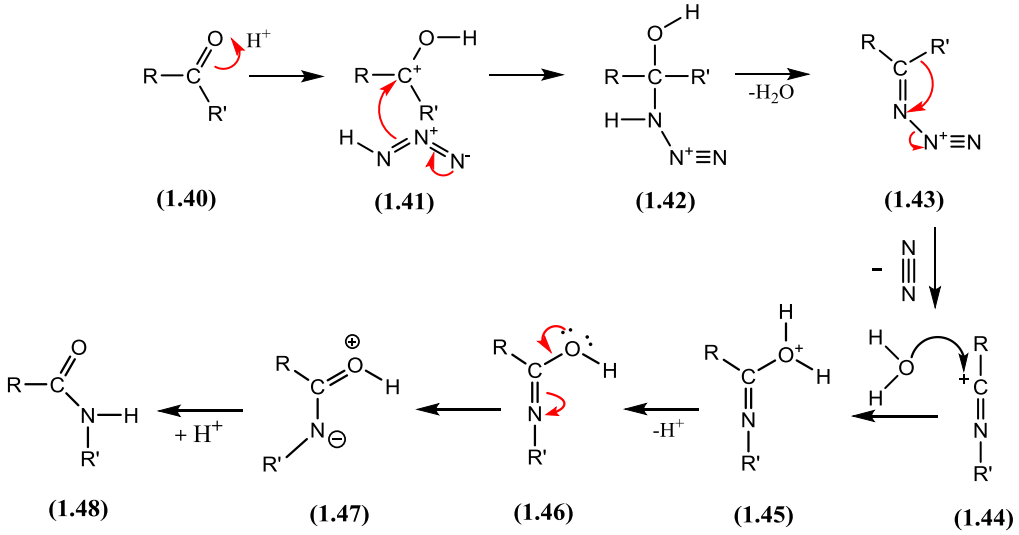


1.3.5 Schmidt Reaction

The Schmidt reaction is the reaction of hydrazoic acid **(1.41)** or an alkyl azide with a carbonyl compound **(1.40)**, alkene, or alcohol, often in the presence of a Brønsted or Lewis acid.[16] This method is similar to the Beckmann rearrangement, since in both reactions the alkyl group migrates from carbon to nitrogen in order to form the amide. Azides are nucleophilic at their terminal nitrogen atoms, and may add to suitably activated electrophiles in the presence of a Brønsted or Lewis acid. Schmidt reaction has considerable utility for the synthesis of hindered or cyclic amides and amines (Schmdit reaction of carboxylic acid yields amine). In the reaction mechanism involving a ketone Schmidt reaction, the carbonyl group is activated by protonation for nucleophilic addition by the azide, forming intermediate **(1.42)**, which loses water in

an elimination reaction to yield imine **(1.43)**, over which one of the alkyl groups migrates from carbon to nitrogen with loss of nitrogen. Attack by water and proton loss converts **(1.44)** to **(1.46)**, which is a tautomer of the final amide **(1.48)** (**Scheme 1.12**).[13] Historically, carbonyl compounds were the first electrophiles successfully employed in Schmidt reaction. Since the initial discovery of the Schmidt reaction, many variants employing alternative electrophiles and hydrazoic acid have been developed.[17] Related reactions of alkyl azides may yield substituted amides, lactams, or amines (after reduction of iminium ions).[18] However, the scope of alkyl azides in the Schmidt reaction is limited compared to hydrazoic acid.

Scheme 1.12: Schmidt Reaction Scheme

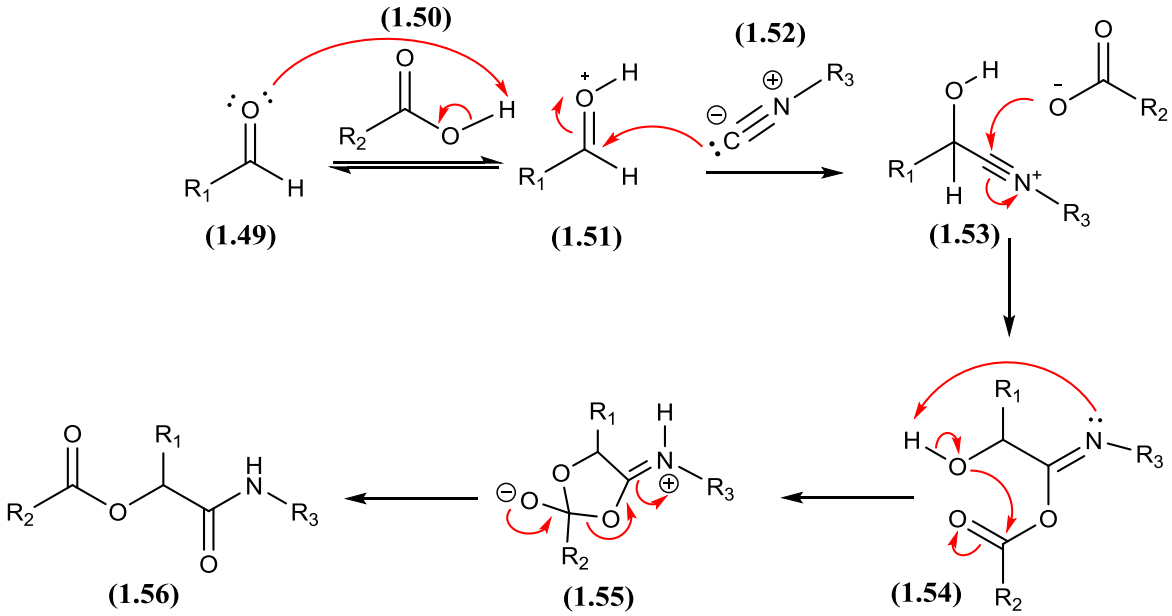


The most common problems with this reaction are site selectivity and tetrazole formation, although the latter can be controlled by changing reaction conditions.[16] To overcome the site selectivity issue, substituted electrophiles can be utilized. However, Steric hindrance to nucleophilic addition lowers the yield of such reactions. Alternatively, the less substituted carbon rarely migrates.

1.3.6 Passerini Reaction

The passerini reaction is a three-component reaction between a carboxylic acid **(1.50)**, a carbonyl compound **(1.49)** such as a ketone or aldehyde, and an isocyanide **(1.49)** which offers direct access to α-hydroxy carboxamides **(1.56)**.[19] Two different reaction pathways have been hypothesized for Passerini reaction: a) Ionic mechanism in presence of polar solvents. In this pathway Passerini reaction proceeds by protonation of the carbonyl group in **(1.49)** followed by nucleophilic addition of the isocyanide **(1.52)** to give the nitrilium ion **(1.53)**. Addition of a carboxylate gives intermediate **(1.54)**. Acyl group transfer and amide tautomerization give the desired ester **(1.56) (Scheme 1.13)**.

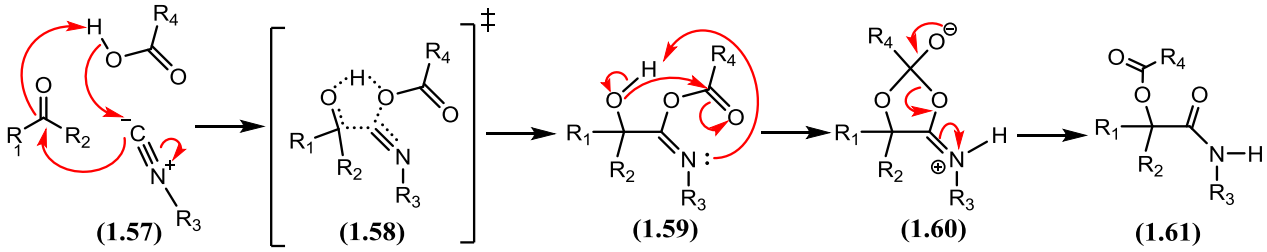
Scheme 1.13: Passerini Ionic Reaction Scheme



b) The other type of mechanism is concerted mechanism which would involve Passerini reaction mechanism in non-polar solvents. This mechanism involves a reaction between the isocyanide **(1.57)**, the carboxylic acid, and the carbonyl in a sequence of nucleophilic additions. The transition state is depicted as a 5-membered ring **(1.58)** with partial covalent or double bonds.

The second step of the Passerini reaction is an acyl transfer to the neighboring hydroxyl group (**Scheme 1.14**).

Scheme 1.14: Passerini Concerted Reaction Scheme



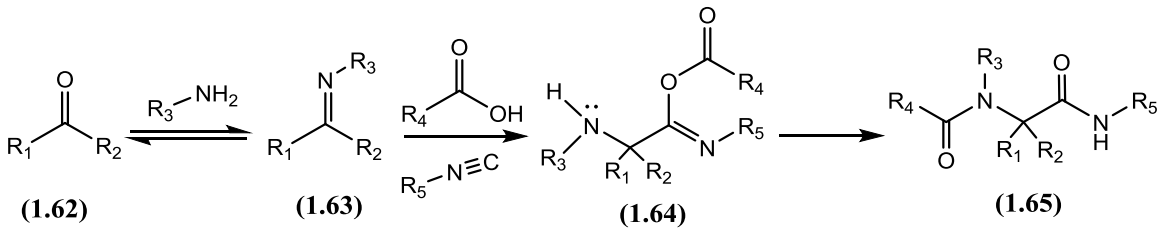
The Passerini reaction proceeds rapidly if the reaction is performed in aprotic solvents at room temperature.[20] High yields are obtained with high concentrations of the starting materials in the reaction mixture. From these findings, it is assumed that the Passerini reaction has more concerted characteristics. Hydrogen bonding is believed to play a crucial role in the formation of the presumed cyclic transition state in concerted mechanism. However, the concerted mechanism is not favorable with respect to the entropy of the reaction. Although, this reaction was found kinetically favored in aprotic solvents (e.g., dichloromethane), recently the mechanism of this reaction has been discussed in various quantum chemical studies to show the true potential pathway among three reactant molecules of Passerini reaction.[20]

1.3.7 Ugi Reaction

The Ugi reaction is a multi-component reaction involving a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to form a bis-amide.[21] Along with the Passerini reaction, it is classified as an isocyanide-based multicomponent reaction which result in formation of α-*N*-acylamino amide. Ugi reaction is widely used in the pharmaceutical industry for preparing different drug compounds. This powerful reaction provides a substituted peptide-like product.[21] The initial

step in the mechanism is the formation of an imine **(1.63)** from the amine and the ketone/aldehyde. Subsequent reaction of the imine **(1.63)** with the isocyanide and the carboxylic acid gives intermediate **(1.64)**, which rearranges via an acyl transfer into the bis-amide **(1.65)** (**Scheme 1.15**).

Scheme 1.15: Ugi Reaction Scheme



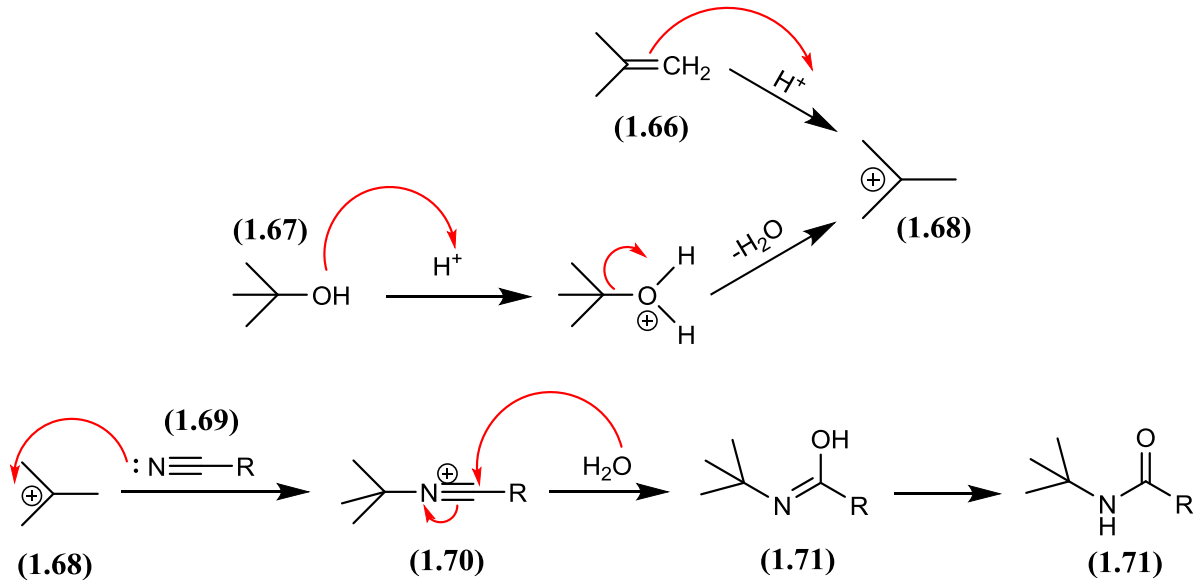
The reaction can also be performed with a pre-formed imine, which results in an increased yield.[21] Although the Ugi reaction has proven to be quite versatile, there are some limitations that become apparent upon examination of the literature. For example, the reaction is widely applicable to a variety of readily available amines, carboxylic acids and aldehydes, but commercial access to isocyanides is more restricted than for the other three components. Additionally, based on industrial demands, it is more desirable to convert initially formed amide into carboxyl derivatives and other functional groups. This concern has been addressed in the traditional Ugi reaction by the invention of a number of so-called convertible isocyanides that can be elaborated after the condensation into various functional groups.[21]

1.3.8 Ritter reaction

The Ritter reaction is an important transformation in organic synthesis which involves amide formation from the reaction of a nitrile **(1.69)** with a substituted alkene **(1.66)** or alcohol **(1.67)** using a stoichiometric amount of strong acid.[22] The Ritter reaction provides a useful method to convert all types of alcohols (secondary, tertiary and benzylic alcohols) or alkenes (suitably substituted alkenes) or tertiary halides to amides by reaction with nitriles in presence of sulfuric

acid as a strong acid. This reaction is typically occurred in highly ionizing solvent, such as AcOH. The known reaction pathway involves the protonation of an alcohol or alkene generating a carbocation **(1.68)**, which adds to a nitrile **(1.69)**, followed by hydrolysis to the corresponding amide **(1.71)** (**Scheme 1.15**).

Scheme 1.16: Ritter Reaction Scheme



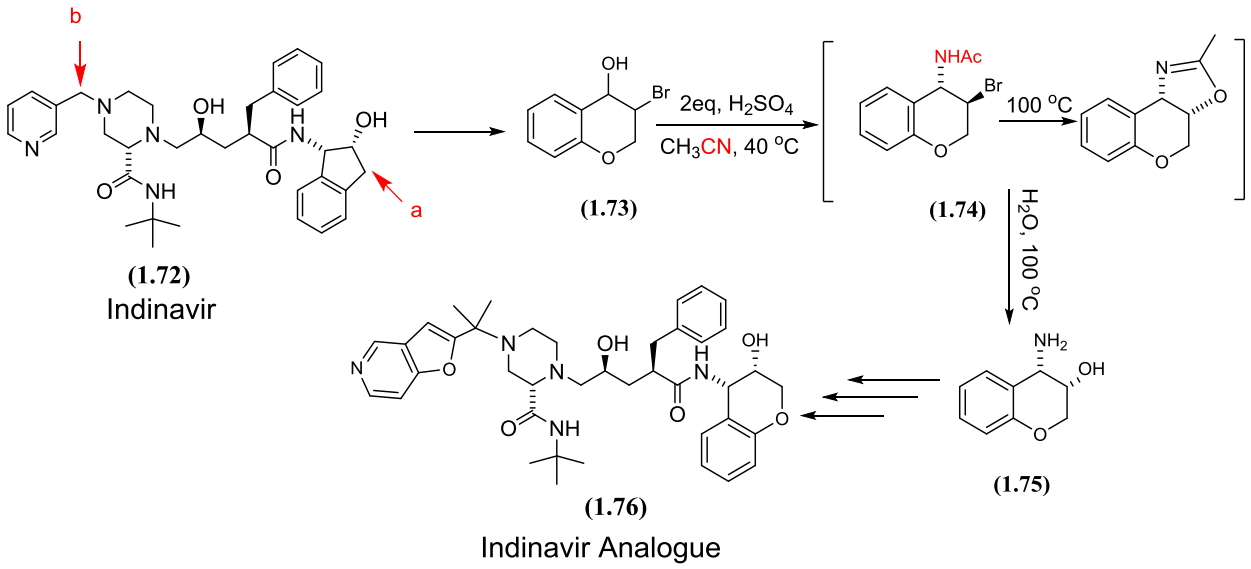
This simple and straightforward procedure first reported by Ritter[22] in 1948 as an efficient way for amide synthesis upon hydrolysis of nitrilium intermediate.

1.4 Applications and Modifications of Ritter Reaction in the Literature

The synthetic route published by Ritter was significantly pragmatic that it has been cited over 600 times by subsequent researchers. Moreover, this reaction has been the subject of several literature reviews.[23-25] Ritter reaction is especially useful for the preparation of bulky amides, which may be hydrolyzed to yield hindered amines. It is also used in industrial processes as it can be effectively scaled up from laboratory experiments to large-scale applications while maintaining

high yield. Real world applications include Merck's industrial-scale synthesis of Indinavir analogue[5] that could be used as a therapeutic reagent for the treatment of HIV infection and AIDS. Although Indinavir **(1.72)** represents a major advance in the management of HIV disease, it suffers from first-pass metabolism and/or food restrictions. The benzylic position of the aminoindanol moiety **(1.72 a)** as well as the pyridine nitrogen and the methylene linker **(1.72 b)** have been identified as the major metabolic sites in Indinavir structure **(Scheme 1.17)**.

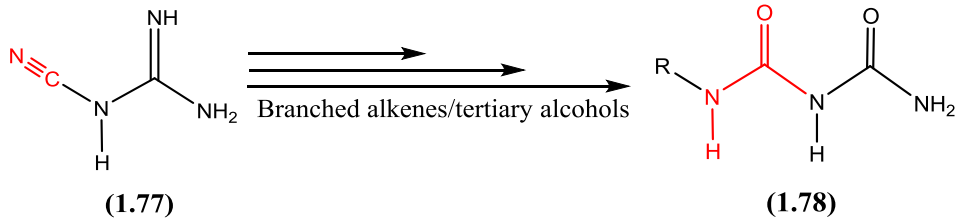
Scheme 1.17: Merck's Industrial-scale Synthesis of Indinavir Analogues[5]



In order to block the metabolic site on the aminoindanol **(1.72 a)** this site was substituted with aminochromanol moiety **(1.75)**. The Ritter reaction is one of the key step in the synthesis of aminochromanol. This conversion provides a second generation of protease inhibitors with better pharmacokinetic parameters and improved activity against resistant viral mutants. Substituted biurets[7] **(1.78)**, effective anticonvulsant drugs with high activity against electroshock, is another example of Ritter reaction application in todays' medical world. The idea of using Ritter reaction for synthesis of such compounds was first considered when researchers started to investigate new compounds with anti-seizure activities. In the search for more effective anticonvulsant drugs,

amides and substituted biurea **(1.78)** have been subjected to thorough examination because they could be visualized as fragments of substituted hydantoins (as effective anti-seizure drugs).

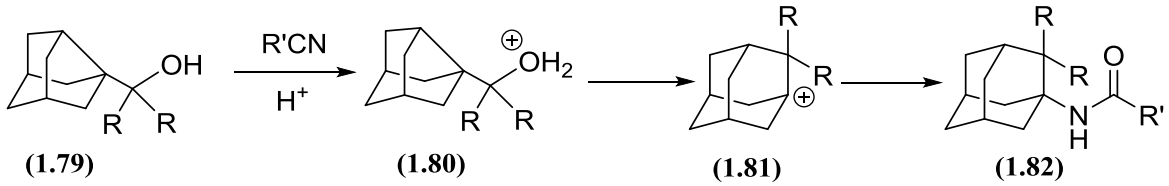
Scheme 1.18: Ritter Reaction Application in Substituted Biuret synthesis



(1.77) **(1.78)**

Adamantine derivatives[6] **(1.82)** which possesses distinct antiviral activity are also synthesized with using the Ritter reaction as one of the critical step in the synthetic pathway.

Scheme 1.19: Ritter Reaction for the Formation of Adamantine Derivatives



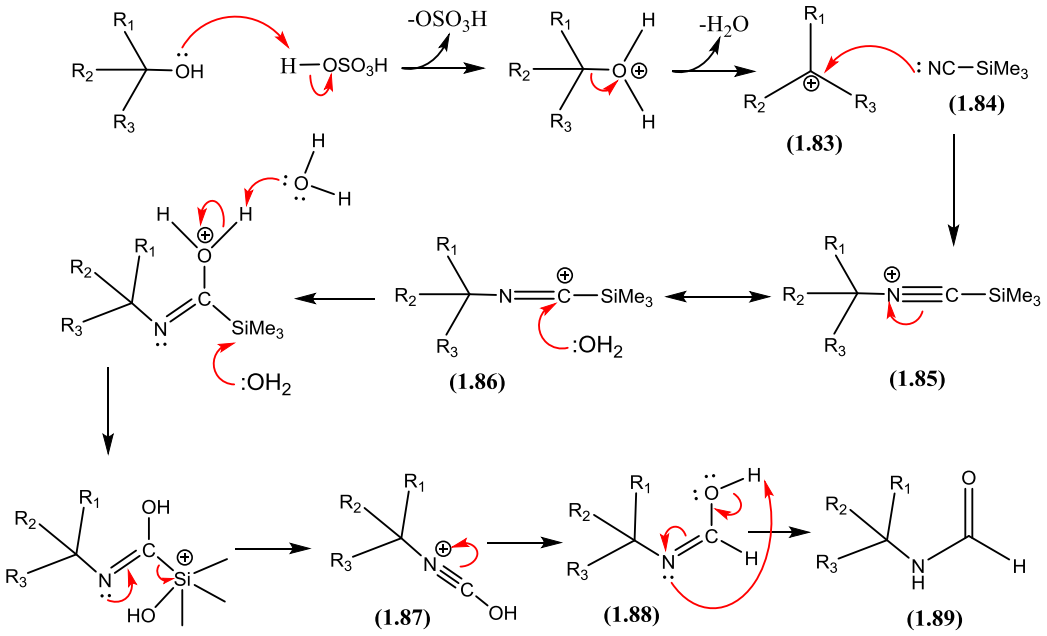
(1.79) **(1.80)** **(1.81)** **(1.82)**

However, despite all of the mentioned applications of traditional Ritter reaction, this reaction suffers from several disadvantages such as large exothermic character of the reaction especially on a large scale, elevated temperatures, harsh reaction conditions, long reaction times, potential rearrangement and side products.[23] The use of an excess amount of corrosive sulfuric acid is the main disadvantage of the classical Ritter reaction due to limited applicability to compounds containing functional groups stable to acid.[24] Despite this limitation, the Ritter reaction has found widespread use in synthesis. Over the years, due to the importance of amides as building blocks in organic and medicinal chemistry and to overcome the above mentioned limitations, several variations have been reported for the Ritter reaction to achieve higher yields with better chemo-selectivity under milder and environmentally acceptable conditions. These variations are discussed below.

1.4.1 Using More Nucleophilic Nitrile in Ritter Reaction

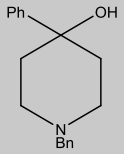
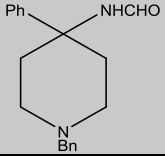
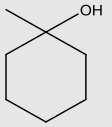
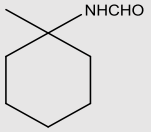
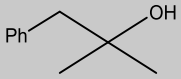
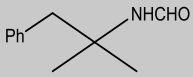
In 1996 a new modification of the Ritter reaction using trimethylsilyl cyanide (Me_3SiCN) **(1.84)** was described, which converts alcohols to their corresponding formamides in high yields.[25] Goel and his coworkers reported that using a more nucleophilic HCN equivalent, such as trimetheylsilyl cyanide (Me_3SiCN has stronger nucleophilic properties based on the alpha-silicon effect) in the Ritter reaction would result in higher yield. Moreover, their reaction pathway is highly exothermic and does not require high temperatures to proceed efficiently to the products. The reaction reported by Goel involves the slow addition of concentrated sulfuric acid to a mixture of an alcohol and trimethylsilyl cyanide. Then the reaction mixture is cooled in an ice bath under inert atmosphere. After the reaction is complete, the mixture is neutralized with NaOH and the formamide product is purified by recrystallization or chromatography.

Scheme 1.20: Modification of Ritter Reaction Using Me_3SiCN



In this pathway secondary alcohols give lower yields than tertiary alcohols, while no reaction is observed with primary alcohols. These observations are consistent with the mechanism involving the protonation of alcoholic -OH group with H_2SO_4 followed by loss of water which gives the carbocation **(1.83)**. Trimetheylsilyl cyanide reacts **(1.84)** quickly with the tertiary carbocation **(1.83),** to form intermediate **(1.86)**, which is then hydrolyzed to the formamide **(1.89)**.

Table 1.1: Examples of Ritter Reaction Using Me_3SiCN[25]

Nitrile (2 equiv)	Alcohol (1 equiv)	Product	Yield (%)
Me_3SiCN			70
Me_3SiCN			86
Me_3SiCN			88

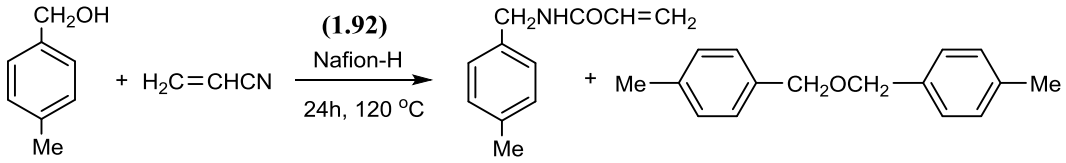
Although this modification in Ritter reaction provides a convenient and useful way to convert tertiary and secondary alcohols to the corresponding formamides and facilitates the rapid synthesis of combinatorial libraries of formamides, this pathway still uses strong and corrosive acid in order to provide desired amides.

1.4.2 Use of Nafion-H as a Solid Catalyst

Nafion-H **(1.92)**, is a perfluorinated sulfonic acid resin which has been used as a superacid catalyst[26] to carry out a variety of acid catalyzed transformations. Yamato reported the Nafion-H catalyzed reactions of benzyl alcohols with nitriles to obtain the corresponding N-benzyl amides.

The reaction of 4-methylbenzyl alcohol **(1.90)** with acrylonitrile **(1.91)** at 120 °C for 24h in the presence of Nafion-H **(1.92)** was investigated. The amount of catalyst required, as a function of the amount of 4-methylbenzyl alcohol **(1.90)**, was between 10 and 30 wt%. Optimum yields of amide were obtained with 30 wt% of catalyst (**Scheme 1.21**).

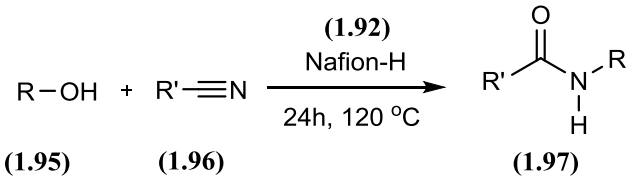
Scheme 1.21: Nafion-H catalyzed Ritter Reaction[26]

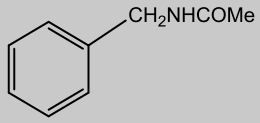
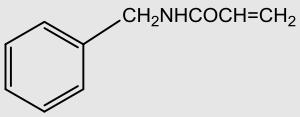
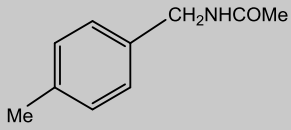
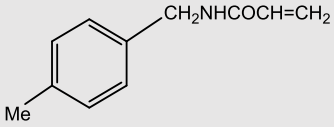


(1.90) **(1.91)** **(1.93)** **(1.94)**

Nafion-H **(1.92)** in catalytic amount was found to be effective in promoting the Ritter reaction of benzyl alcohols with nitriles such as acetonitrile, acrylonitrile or benzonitrile to give the corresponding *N*-benzylamides.[26] The Ritter reaction is often carried out with a large excess of concentrated sulfuric acid, so prompting this reaction under catalytic conditions could be considered as an improvement in reaction pathway. Using Nafion-H can eliminate the use of corrosive sulfuric acid. In addition, the environmental difficulties that arise from using a large excess of acid (like acid rain, marine life issues) could be solved. The major advantage with Nafion-H is the simple work-up procedure, wherein the product is isolated by filtration of the catalyst followed by evaporation. Furthermore, the ready regeneration of the catalyst without the loss of catalytic activity offers an advantage over other Ritter reaction modifications. In this method no acid-catalyzed polymerization of acrylonitrile was observed under the reaction conditions in contrast to other acid-catalyzed Ritter reaction

Table 1.2: Examples of Nafion-H catalyzed Ritter Reaction[26]



(1.96) (1 equiv)	(1.95) (1 equiv)	Product (1.97)	Yield (%)
CH_3CN	benzyl alcohol		39
CH_2=CHCN	benzyl alcohol		56
CH_3CN	4-methylbenzyl alcohol		49
CH_2=CHCN	4-methylbenzyl alcohol		43

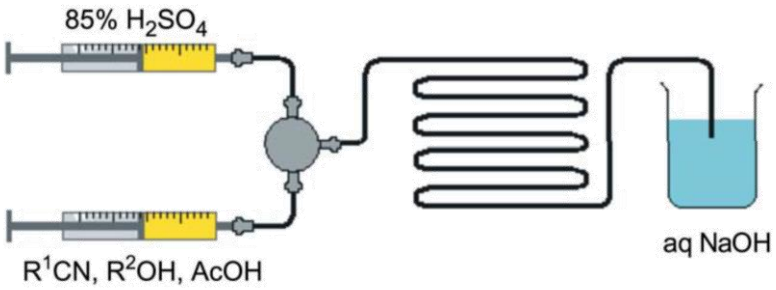
Despite all of the advantages of Nafion-H catalyzed Ritter reaction, this method suffers from low yields (30-50%) and high temperature (120 °C). In addition, since the yield of reaction depends on the amount of Nafion-H catalyst that is used in the course of reaction, for higher yield larger amounts of catalyst is needed which adds to the cost of this reaction.

1.4.3 Using Microfluidic Device-based Ritter Reaction

Efficient mixing, temperature control and small environmental exposures allow reactions carried out in microfluidic devices to perform superior to their batch-type counterparts in conventional flasks.[28] One of the key advantages of microflow procedures in synthetic chemistry

is the superior kinetic and thermodynamic control over the course of a reaction when compared to the batch process. Mixing in microfluidic devices has been proven to be much more efficient and quicker than even rapid stirring in a flask. Additionally, the dimensions of the microstructured devices together with the flow rate can allow very short and very accurately adjusted reaction times. Thermodynamic control is facilitated as the large surface to volume ratio of the microreactor leads to optimal temperature exchange between the surrounding heat/cold source and the reactor. The Ritter reaction has been optimized for flow conditions.[28] Use of a microfluidic-type Ritter reaction lead to shorter reaction times with higher yields and also is advantageous with regards to safety, productivity, and tolerance towards substrate functionalities.

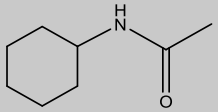
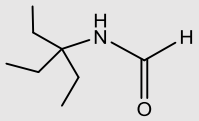
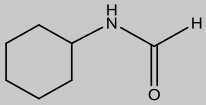
Figure 1.1: Ritter Reaction in Flow



As concentrated sulfuric acid is used in microfluidic-based Ritter reaction, PEEK tubing and mixers were not compatible. Teflon micromixers were shown to be much more reliable for these reaction conditions, and they show long-term reliability as well. The Ritter reaction in microfluidic device is performed at 90 °C. Use of nitrobenzene, dioxane and acetic acid as solvent all led to clean conversion without notable side products, but it appeared that acetic acid required much shorter reaction times. The use of cyanides appears to be particularly promising in micro-reactor chemistry because they offer a safe alternative to the hazards in the large-scale batch use of nitriles and heat. This method is especially suitable for the synthesis of formamides. The formamides

produced in these reactions are of high value as they can easily be cleaved. Additionally, tertiary alcohols reacted readily and cleanly under the optimized conditions and afforded the corresponding amides in reasonable yields with fast reaction times and more safely than in a batch process. Although under microfluidic conditions we can achieve fast synthesis of amides and formamides by minimizing the hazards involved in the classical Ritter reaction, this technique is extremely expensive and presence of strong acidic conditions is still a challenging subject for micro-reactor technology.

Table 1.3: Examples of Ritter Reaction Under Microfluidic Condition[28]

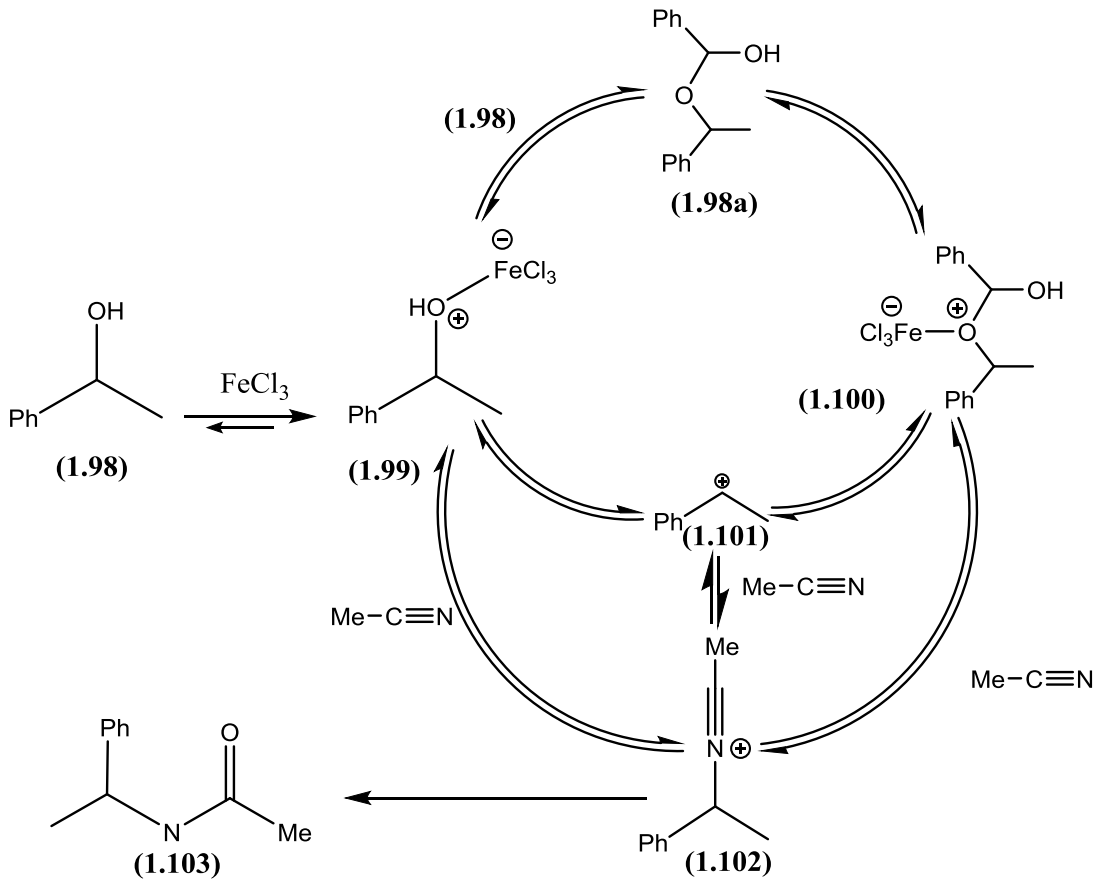
Nitrile (1 equiv)	Alcohol (1 equiv)	Product	Temp (ºC)	Time (hr)	Yield (%)
MeCN	cyclohexanol		85	2	69
NaCN	3-ethyl-3-pentanol		85	2	64
NaCN	cyclohexanol		45	2	63

1.4.4 Replacing Sulfuric Acid by Metal Complexes

The Ritter reaction may be catalyzed by metal complexes like cobalt(II) chloride[29] or chromium tricarbonyl complexes.[30] Nevertheless, the main disadvantages of these procedures are the use of toxic catalysts that cannot completely eliminate the need for strong protic acid. As it was recently demonstrated that $FeCl_3$ is able to activate benzylic alcohols to produce carbocation intermediates, Reymond and his coworkers have envisaged to synthesize amides from benzylic alcohols or *t*-butyl acetate by using a Ritter reaction catalyzed by $FeCl_3$.[24] According to their results, it can be speculated that amide **(1.103)** can come from ether **(1.98a)** as the latter can be polarized by

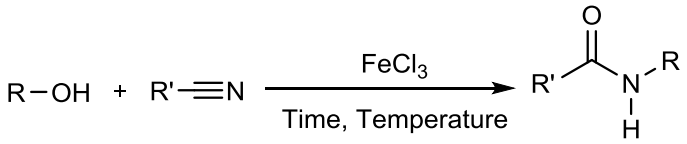
$FeCl_3$ to generate the benzylic carbocation **(1.101)** which can be trapped by MeCN. However, we cannot exclude that **(1.99)** or **(1.100)** can be attacked by MeCN to produce **(1.102)**, or that **(1.99)** can generate the carbocation **(1.101)** directly (**Scheme 1.22**).

Scheme 1.22: **$FeCl_3$-catalyzed Ritter reaction**

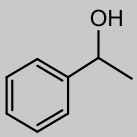
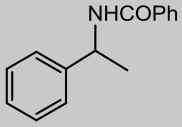
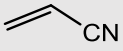
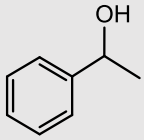
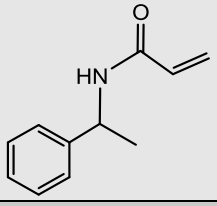
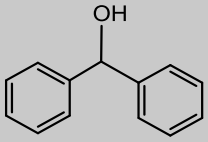
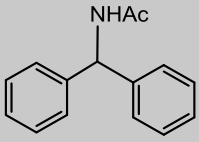
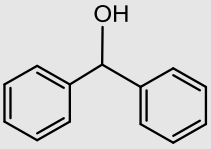
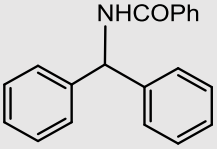


Although this catalytic reaction is an inexpensive and eco-friendly process allowing for the preparation of various amides that can be useful synthons, it suffers from high temperature (150 °C). Moreover, according to the experimental data, $FeCl_3$-catalyzed Ritter reaction is not applicable to a wide range of nitriles, therefore the application is not widespread. Benzonitrile, acrylonitrile and acetonitrile worked the best in reaction with benzylic alcohols in presence of $FeCl_3$ as the catalyst.

Table 1.4: Examples of $FeCl_3$-Catalyzed Ritter Reaction. (10% mol of $FeCl_3$)[24]



(1.104) **(1.105)** **(1.106)**

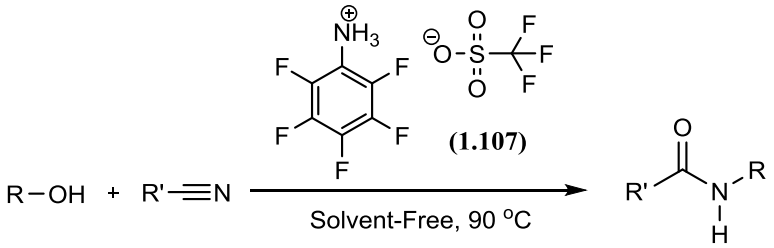
(1.105) (10 equiv)	(1.104) (1 equiv)	Product (1.106)	Time	Temp (°C)	Yield (%)
PhCN			24	150	54
			12	150	66
MeCN			24	120	96
PhCN			24	150	75

1.4.5 Replacing Sulfuric Acid by Organocatalysts

However, the $FeCl_3$-catalyzed Ritter reaction reported by Reymond was not suitable for drug synthesis.[24] A new method for Ritter reactions using metal-free Lewis acid catalysts for designing suitable drugs was needed. Khaksar has developed a simple chemoselective methodology for a modified Ritter reaction using organocatalyst.[31] In contrast to the methods using potentially hazardous metal catalysts, this method offers some advantages, for example organocatalysts have gained importance due to the economic and environmental considerations. These catalysts are generally less expensive, highly reactive, eco-friendly, easy to handle, reduce reaction times,

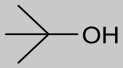
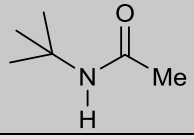
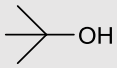
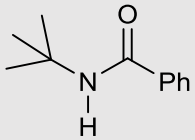
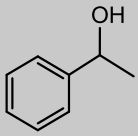
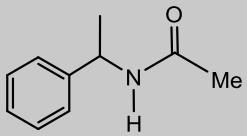
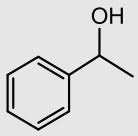
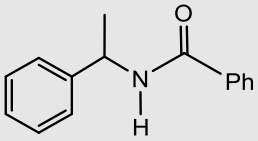
impart greater selectivity, and can be applied under less demanding reaction conditions, such as rigorously anhydrous or anaerobic conditions.[24,31] Pentafluorophenylammonium triflate (PFPAT) **(1.107)** has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity, stability to air, and water tolerance. Khaksar and his coworkers attempted Ritter reaction of various nitriles with alcohols using PFPAT (**Scheme 1.23**).

Scheme 1.23: General Scheme of Ritter Reaction Using PFPAT[31]



PFPAT **(1.107)** is easy to prepare from commercially available pentafluoroaniline and triflic acid. Short reaction times, ease of product isolation/purification, and low costs are among the important advantages of this technique using PFPAT **(1.107)**. Despite all of these advantages this method is not applicable to all types of alcohols and the catalyst is decomposed during workup, which makes the whole process more expensive. Moreover, stoichiometric amounts of PFPAT **(1.107)** were preferred for this functional transformation to optimize yields.

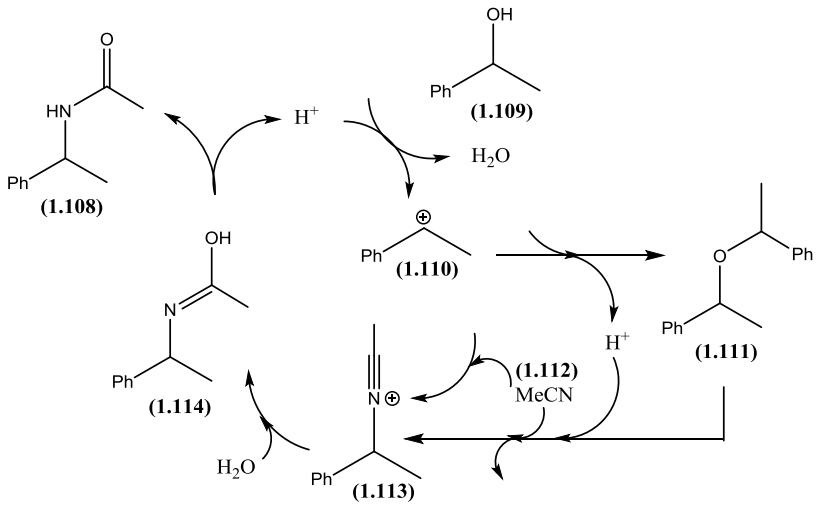
Table 1.5: Examples of Ritter Reaction in Presence of PFPAT

Nitrile (2.0 equiv)	Alcohol (2.2 equiv)	Product	Yield (%)
MeCN			90
PhCN			90
MeCN			95
PhCN			92

1.4.6 Organic Brønsted Acid-mediated Ritter Reactions

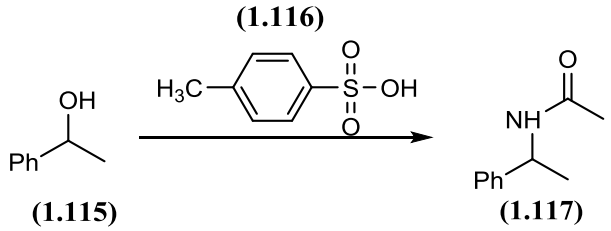
In principle, the Ritter reaction is expected to proceed through a catalytic cycle using a strong acid. As mentioned before, the standard conditions to perform this reaction involve the use of stoichiometric amounts of concentrated sulfuric acid or a substance that could react as a strong acid. The reaction of a benzylic alcohol such as **(1.109)** with an acid forms the carbocation **(1.110)**. This is trapped with a molecule of acetonitrile **(1.112)** to generate the nitrilium cation **(1.113)**, which is captured by the water produced in the first step of the process to afford **(1.114)** regenerating a molecule of acid. So, in principle, the acid could be used in a catalytic amount **(Scheme 1.24)**.

Scheme 1.24: Proposed Catalytic Cycle for Ritter Reaction[32]



However, as mentioned before, the standard conditions to perform the reaction involve the use of stoichiometric amounts of concentrated sulfuric acid. Although in the past some alternative methodologies have been developed for the Ritter reaction where sulfuric acid is replaced by metal complexes[33], triflic anhydride[34], $BF_3 \cdot Et_2O$[35], or immobilized reagents on solid supports,[36] most of these methods suffer from drawbacks such as the use of compounds that are corrosive, toxic, or expensive, whereas others involve anhydrous conditions. These drawbacks motivated researchers to investigate new types of acidic catalysts. In this context, Sanz and his group have found that simple Brønsted acid like *p*-toluenesulfonic acid (TsOH) **(1.116)** is able to catalyze the direct nucleophilic substitution of propargylic alcohols as well as benzylic and allylic ones[32] (**Scheme 1.25**).

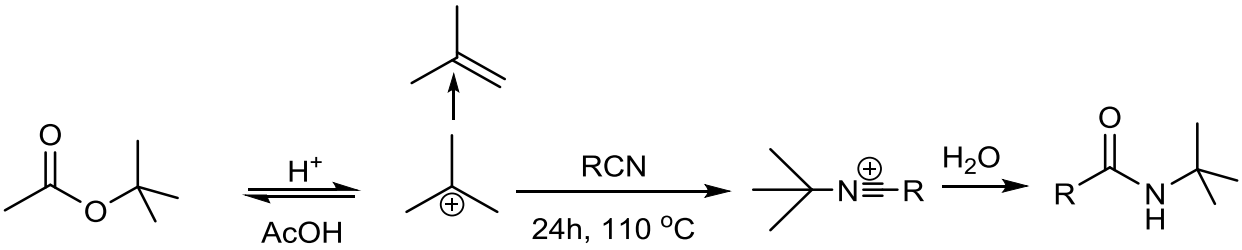
Scheme 1.25: Ritter Reaction Under Catalytic Organic Brønsted Acid Condition



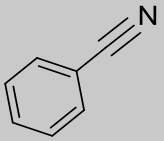
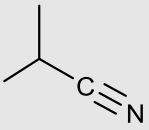
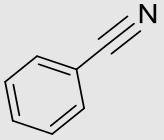
1.4.7 Using Acetate Species as Alternative Reagents for Alcohols/Alkenes

In the traditional Ritter reaction, either isobutylene or *t*-butanol in the presence of acid is employed to generate the *t*-butyl cation. In spite of this widely used method, some inherent problems exist; for example, isobutylene is a highly flammable gas and there have been reports of exothermic events when used in Ritter reaction.[37] A cationic polymerization of isobutylene is a likely cause for these exothermic events. Another complication involving the use of *t*-butanol is due to its low melting point which makes it a semi-solid at room temperature. Alternatively, *t*-butyl acetate **(1.118)** could be used as a reagent because of its ease of handling, ready availability, low cost, and providing better leaving group compared to *t*-butanol.[38] However, there are only limited examples of Ritter reactions in which *t*-butyl acetate **(1.118)** is employed to generate the *t*-butyl cation **(1.68)**. This idea was first examined in 2009 by Milne in R&D center of Amgen Inc. [29] They evaluated a wide variety of acids and co-solvents for this reaction. Even during their study, sulfuric acid was still the best choice which resulted in full conversion and good assay yields (>80%). Slow addition of sulfuric acid in acetic acid to a mixture of the substrate, and *t*-butyl acetate in acetic acid at 30 °C gave a clean reaction profile (**Scheme 1.26**).

Scheme 1.26: Ritter Reaction from *t*-Butyl Acetates[38]



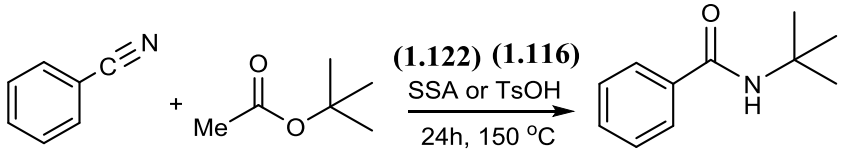
(1.118) **(1.119)** **(1.68)** **(1.120)**

Nitrile (1 equiv)	Temperature (°C)	Yield (%)
	110	90
	110	65
	130	72
	125	92

In 2016 another example of a Ritter reaction was reported in which *t*-butyl acetate **(1.118)** and benzyl acetate were employed to generate the corresponding *t*-butyl or benzyl cation[28]. Esfahani and his coworkers have reported the formation of *N*-t-butylbenzamide **(1.123)** which utilized the reaction of *t*-butyl acetate **(1.118)** with benzonitrile **(1.121)** (**Scheme 1.27**). Solid acid catalysts, especially heteropoly acids play a key role in recently reported Ritter reaction of acetates. Silica sulfuric acid (SSA) **(1.122)**, a re-usable heterogeneous solid catalyst that is easily prepared by

treatment of silica gel with chlorosulfonic acid at room temperature, and *p*-toluenesulfonic acid (TsOH) **(1.116)**, a strong organic acid has been utilized as catalysts in such reactions. Using such catalysts has its own advantages and drawbacks. They are eco-friendly and are important toward the development of green technologies for environmental safety. However, these types of catalysts introduce additional cost to the reaction and they are not as efficient as sulfuric acid. Moreover, using higher temperature compared to the traditional Ritter reaction is another drawback of Ritter reaction of acetate species.

Scheme 1.27: Formation of *N*-t-Butylbenzamide Using *t*-Butyl Acetate



(1.121) **(1.118)** **(1.123)**

(Yield: 91%)

1.5 New Approach Toward Ritter Reaction

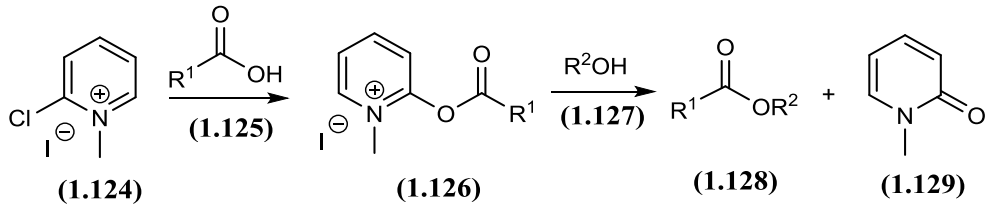
Ritter reactions have been known for many years as an important methodology for amide synthesis. However, despite its obvious utility its application has been limited due to some important drawbacks like harsh reaction conditions, difficulty with stereochemical control, and use of an excess amount of corrosive sulfuric acid.[23-25] Over the years, due to the importance of amides in organic chemistry and to overcome the previously mentioned limitations, several variations have been reported for the Ritter reaction to achieve higher yields under milder and environmentally acceptable conditions. Although the modified methods which were discussed earlier in section **1.4**, offer better chemo-selectivity and environmentally more acceptable conditions, some of them suffer from at least one of the following issues: limited availability of

reagent,[26] uses hygroscopic reagents[23], low yield, tedious product isolation, longer reaction time and competing side reactions. Therefore, the focus of this research project was to explore the utility of oxypyridinium salt for synthesis of *N*-benzyl amides as an attractive alternative for Ritter reaction. More specifically, the aim of this research was to use the reagent 2-Benzyloxy-1-methylpyridinium triflate (BnOPT) **(1.134)** for amide synthesis under relatively neutral conditions. This reagent allows for benzyl group transfer without the need for strong acids or bases required for traditional routes.[39-41]

1.5.1 Development of 2-Benzyloxy-1-methylpyridinium triflate (BnOPT)

Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide **(1.124)**, is one of the most valuable reagents for activation of hydroxyl groups of carboxylic acids and alcohols. It is a pale yellow crystalline solid which is stable at room temperature in closed containers under normal storage and handling.[42,43] **(Scheme 1.28)**

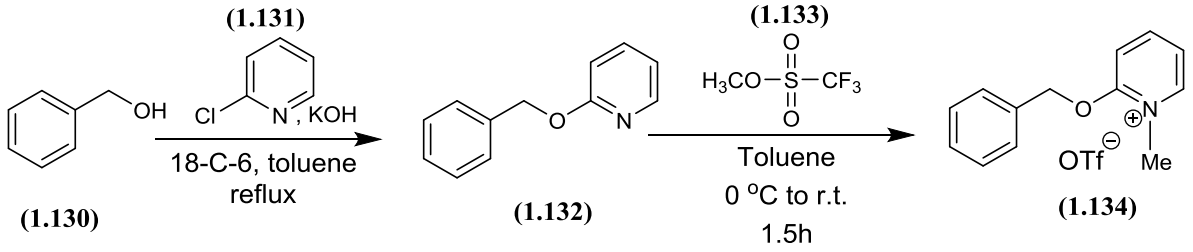
Scheme 1.28: Esterification Reaction with Mukaiyama's Reagent



Mukaiyama's reagent contains a pre-activated nitrogen with no need for acidic additives. This characteristic could be used as a driving force for esterification. This reaction begins with a nucleophilic aromatic substitution reaction between Mukaiyama's reagent and a carboxylic acid **(1.119)** to activate the –OH group. The addition of an alcohol **(1.127)** to the carbonyl in **(1.126)** is followed by elimination of pyridone **(1.129)** to generate the ester **(1.128)**. Building off this concept, Dudley developed a benzyl transfer reagent known as 2-benzyloxy-1-methylpyridinium triflate (BnOPT) **(1.134) (Scheme 1.29)** by reacting benzyl alcohol **(1.130)** with 2-chloropyridine **(1.131)**,

using potassium hydroxide (KOH) as a base and 18-crown-6 as a catalyst, in toluene for an hour at reflux (111 °C) to generate 2-benzyloxypyridine **(1.132)** which is then reacts with methyl triflate (MeOTf) **(1.133)** in toluene at 0 °C for one and half hours to form BnOPT **(1.134)**.[39] **(Scheme 1.29)**. Similar to Mukaiyama's reagent, BnOPT **(1.134)** contains a pre-activated nitrogen that can be used as a driving force for benzyl cation formation.

Scheme 1.29: Synthesis of 2-benzyloxy-1-methylpyridinium triflate (BnOPT)



1.5.2 Application of BnOPT

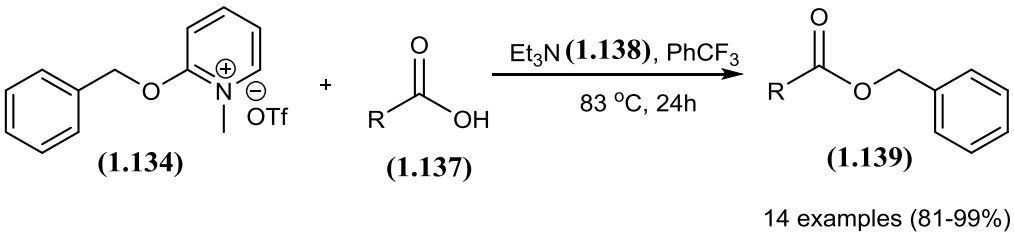
To date, BnOPT has been shown to be an effective reagent to transfer a benzyl group upon warming to nucleophiles including alcohols and carboxylic acids. BnOPT allows for benzyl group transfer without the need for strong acids or bases required for traditional routes. The fact that BnOPT is a bench stable salt that can be synthesized and stored on the large scale is an important advantage that makes it potentially possible to expand the utility of this reagent. BnOPT has successfully transferred benzyl groups to alcoholic functional groups in order to form benzyl ethers.[39-41] Using BnOPT **(1.134)**, the formation of benzyl ethers **(1.136)** is achieved in the presence of magnesium oxide (MgO), in trifluorotoluene ($PhCF_3$) for 24 h at 83 °C.[39,40] With this methodology, the benzylation of alcohols is now possible under milder conditions without strong acids, strong bases, or excessive heating. MgO which is present in this reaction, serves as an acid scavenger as opposed to a strong base due to its insolubility in the reaction conditions. Pyridone

(1.129) is a byproduct of this reaction which is easily removed as a hydroxypyridinium salt following protonation during an aqueous workup.

Scheme 1.30: Synthesis of Benzyl Ethers using BnOPT

BnOPT **(1.134)** can also transfer a benzyl group to a carboxylic acid **(1.137)** in order to yield benzyl esters **(1.139)** under mild conditions.[44] This reaction can serve as an alternative for Fischer esterification. Optimized conditions for the formation of benzyl esters **(1.139)** includes 2 equivlents of BnOPT **(1.134)** which is reacted with a carboxylic **(1.137)** acid in presence of 2 equivalents of trimethylamine (Et_3N) **(1.138)** serving as a base in trifluouotoluene at 83 °C for 24h.

Scheme 1.31: Mechanism for the Synthesis of Benzyl Ethers Using BnOPT

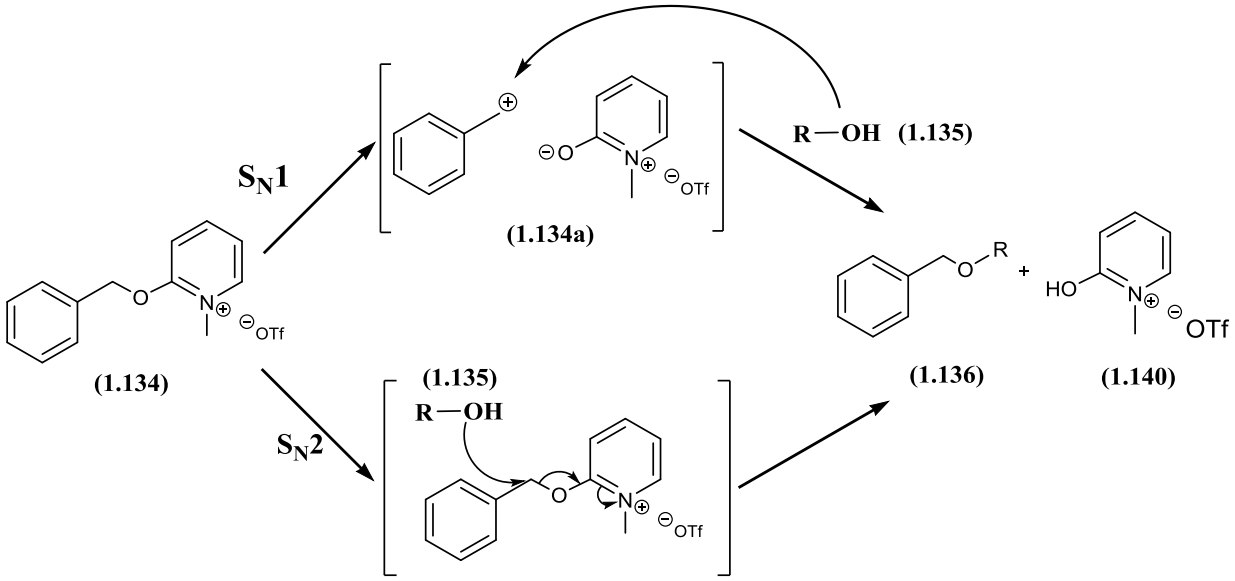


Et_3N is a weak base which is important for the optimal conditions which is added to reduce the reaction time and optimize yields. Its role is to coordinate to the acidic hydrogen of carboxylic acid to activate it as a stronger nucleophile. Et_3N also serves as a benzyl cation scavenger to prevent the formation of a dibenzyl ether byproduct.

1.5.3 Exploring the Mechanism for Benzyl transfer using BnOPT

Understanding the mechanism of a reaction allows a chemist to adjust parameters and alter the starting materials to obtain a highly specific product. The benzylation of alcohols by BnOPT is the result of a substitution reaction. There are two potential mechanistic extremes for nucleophilic substitution reactions, S_N1 and S_N2 **(Scheme 1.32)**. In the top pathway, an S_N1 reaction proceeds as BnOPT **(1.134)** decomposes to yield a benzyl carbocation **(1.134a)** and pyridone. Subsequent attack by nucleophile **(1.135)** results in benzyl ether **(1.136)** formation. Alternatively, in the bottom pathway, an S_N2 reaction takes place as the alcohol **(1.135)**, serving as a nucleophile, attacks BnOPT **(1.134)** resulting in the loss of a leaving group (*i.e.* pyridone) in a concerted fashion to generate the benzyl ether **(1.136)**.

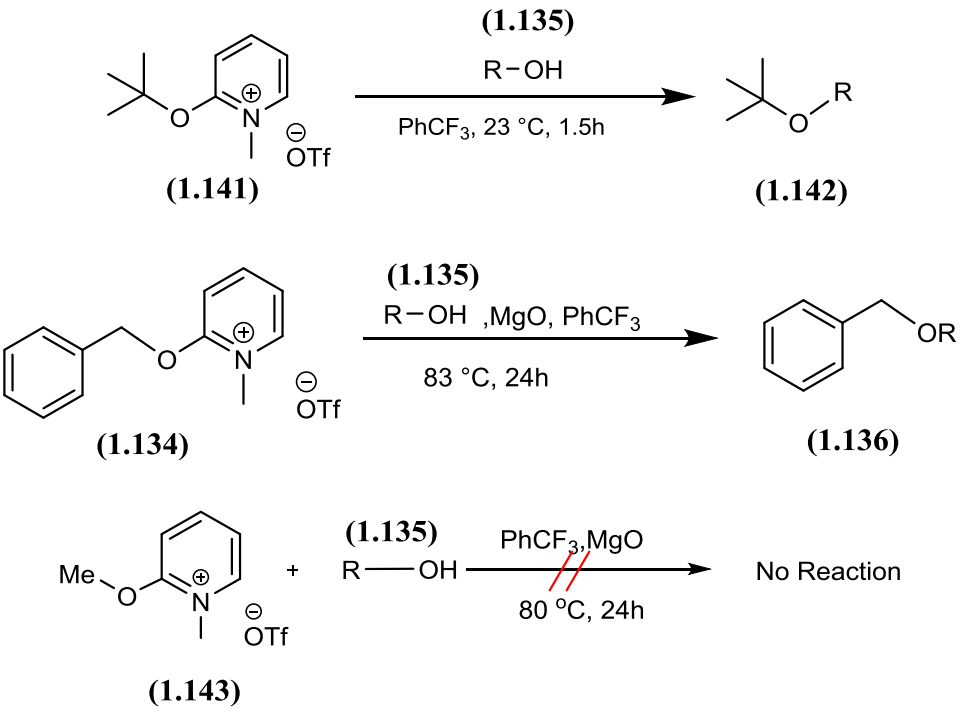
Scheme 1.32: S_N1 **vs.** S_N2 **Pathways**



Previous studies support a more S_N1-like pathway for the generation of benzyl ethers **(1.136)** using BnOPT **(1.134)** as shown in **Scheme 1.32**. Support of a predominantly S_N1-like pathway came from studies in which the benzyl group of BnOPT was replaced with a *t*-butyl group **(Scheme 1.33)** to generate 2-*t*-butoxy-1- methylpyridinium triflate[45] **(1.141)**. This salt is a tertiary substrate

which is inaccessible to the regioselective backside attack by the alcohol that is required for an S_N2-type reaction to take place; therefore, the decompostion of the salt to generate a tertiary carbocation via a S_N1 pathway is the only possibility as far as substitution reactions are concerned. This carbocation is subsequently trapped by an alcohol **(1.135)** to generate the corresponding *t*-butyl ether **(1.142)**. The lower time and temperature required for this reaction (23 °C, 1.5h) indicates that the transition state is more stable and lower in energy; therefore, less energy is needed to get over the activation barrier. Similarly, the reaction went to completion in 1.5h; whereas, the formation of benzyl ethers **(1.136)** with BnOPT **(1.134)** took 24h to reach completion. The slow step, or rate-determining step, in an S_N1 reaction is the formation of the carbocation which is followed by a rapid nucleophilic attack. The decrease in reaction time and temperature when comparing the formation of a benzyl carbocation to a more stable tertiary carbocation provides support of a S_N1-like mechanism. Reactions attempted with the methyl analog of BnOPT **(1.134)** offered further support for a S_N1-like mechanism. In this case, the benzyl group of BnOPT was replaced with a methyl group for the formation of a methyl ether. This methyl analog of oxypyridinium salt **(1.143)** can only proceed through an S_N2-type reaction for two reasons: 1) methyl carbocations are very unstable, 2) the lack of steric hinderence allows for an unimpeded nucleophilic backside attack to an easily accessible carbon. Subjecting **(1.143)** to identical conditions for the formation of benzyl ethers was unsuccessful with no methyl ether formation after 24h **(Scheme 1.33)**. This observation discredits an S_N2 mechanism for benzyl ether formation.

Scheme 1.33: Supports of S_N1 Mechanism

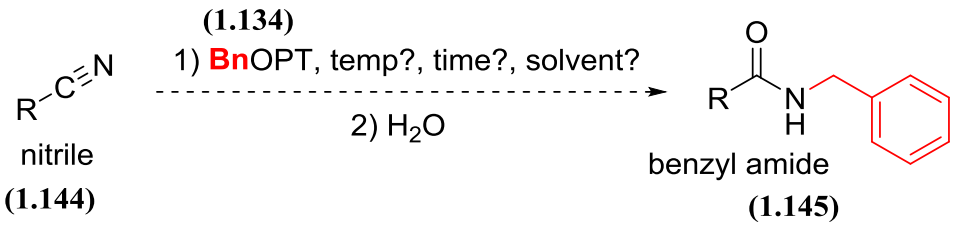


1.5.4 Expanding the Utility of Oxypyridinium Salt to Transfer Benzyl Groups to Nitriles

The successful transfer of a benzyl group from the pyridinium moiety of BnOPT to alcohols and carboxylic acids motivated further investigation of oxypyridinium salts as benzyl transfer reagents. The use of nitriles **(1.144)** as nucleophiles in reactions with BnOPT **(1.134)** would afford benzyl amides **(1.145)** upon quenching with water which are quite useful to synthetic and medicinal chemists. Nitriles are weaker nucleophiles than alcohols and activated carboxylic acids due to the different hybridization. Nitriles have sp hybridized orbitals while alcohols have sp^3 and carboxylic acids have sp^2 hybridized orbitals. The sp hybridized orbitals have more s-orbital characteristics than sp^2 and sp^3 hybridized orbitals so they are closer to the nucleus. Therefore, the electrons in an sp hybridized orbital experience greater stabilization from the protons in the nucleus making them less reactive. Previous experiments indicated that the formation of a stable carbocation like tertiary carbocation was a requirement for the benzyl group

being transferred from the oxypyridinium moiety. However, no previous study investigates formation of a nitrilium ion using an oxypyridinium salt. The transfer of a benzyl group from the pyridinium moiety to nitrile functional groups appears to be an appropriate alternative for Ritter reaction to make amides under milder conditions with widespread applications. The focus of this research project is to investigate the capability of different oxypyridinium salts in transferring benzyl group to the nitrile derivatives **(1.144)** with the aim of *N*-benzyl amide **(1.145)** synthesis.

Scheme 1.34: Proposed Ritter Reaction Using BnOPT



References

(1) DeRuiter, J. Amides and Related Functional Groups. *Princ. Drug Action* **2005**, *1*, 1–16.
(2) Montalbetti, C. A. G. N.; Falque, V. Amide Bond Formation and Peptide Coupling. *Tetrahedron* **2005**, *61* (46), 10827–10852.
(3) Su, H. C. F.; Horvat, R. Isolation, Identification, and Insecticidal Properties of Piper Nigrum Amides. *J. Agric. Food Chem.* **1981**, *29* (1), 115–118.
(4) Anavi, M.; Zilkha, A. The "Ritter" Reaction on Polymers. *Eur. Polym. J.* **1969**, *5* (1), 21–28.
(5) Cheng, Y.; Zhang, F.; Rano, T. A.; Lu, Z.; Schleif, W. A.; Gabryelski, L.; Olsen, D. B.; Stahlhut, M.; Rutkowski, C. A.; Lin, J. H. Indinavir Analogues with Blocked Metabolism Sites as HIV Protease Inhibitors with Improved Pharmacological Profiles and High Potency against PI-Resistant Viral Strains. *Bioorg. Med. Chem. Lett.* **2002**, *12* (17), 2419–2422.
(6) Klimochkin, Y. N.; Moiseev, I. K.; Boreko, E. I.; Vladyko, G. V; Korobchenko, L. V. Synthesis and Antiviral Activity of Nitrogen-Containing Adamantane Derivatives. *Pharm. Chem. J.* **1989**, *23* (4), 304–307.
(7) Dunnigan, D. A.; Close, W. J. Anticonvulsant Drugs. VI. Some 1-Substituted Biurets1. *J. Am. Chem. Soc.* **1953**, *75* (15), 3615–3616.
(8) Scheme, B. G. R. Schotten-Baumann Reaction. *Compr. Org. Name React. Reagents* **2010**, *573*, 2536–2539.
(9) Li, J. J. Schotten-Baumann Reaction. In *Name Reactions*; Springer, **2002**; p 329.
(10) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed.; Oxford University Press, **2012**.
(11) J. C. Sheehan and G. P. Hess. A New Method of Forming Peptid Bond. *J. Am. Chem. Soc.* **1955**, 77, 1067.
(12) Kim, M. H.; Patel, D. V. *Tetrahedron Lett.* **1994**, 35, 5603-5606.
(13) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219-1222.
(14) El-Faham, A; Subiró-Funosas, R; Prohens, R; Albericio, F. *Chem. Eur. J.*, **2009**, 15, 9404-9416.
(15) De Luca, L.; Giacomelli, G.; Porcheddu, A. Beckmann Rearrangement of Oximes under Very Mild Conditions. *J. Org. Chem.* **2002**, *67* (17), 6272–6274.
(16) Wolff, H. The Schmidt Reaction. *Org. React.* **1946**, *3* (8), 307–336.
(17) Gu, P.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Rapid Access to Fused Polycyclic Nitrogen-Containing Heterocycles via a Multistep One-Pot Transformation. *Org. Lett.* **2012**, *14* (22), 5796–5799.
(18) Motiwala, H. F.; Charaschanya, M.; Day, V. W.; Aube, J. Remodeling and Enhancing Schmidt Reaction Pathways in Hexafluoroisopropanol. *J. Org. Chem.* **2016**, *81* (4), 1593–1609.
(19) Banfi, L.; Riva, R. The Passerini Reaction. *Org. React.* **2005**, *65* (1), 1–140.
(20) Ramozzi, R.; Morokuma, K. Revisiting the Passerini Reaction Mechanism: Existence of the Nitrilium, Organocatalysis of Its Formation, and Solvent Effect. *J. Org. Chem.* **2015**, *80* (11), 5652–5657.

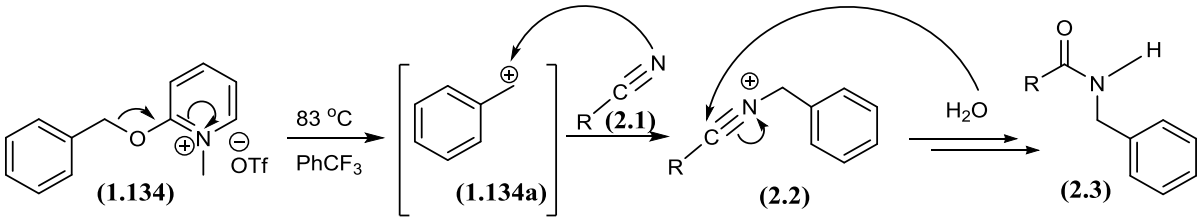
(21) Marcaccini, S.; Torroba, T. The Use of the Ugi Four-Component Condensation. *Nat. Protoc*. **2007**, *2* (3), 632–639.
(22) Ritter, J. J.; Minieri, P. P. A New Reaction of Nitriles. I. Amides from Alkenes and Mononitriles1. *J. Am. Chem. Soc.* **1948**, *70* (12), 4045–4048.
(23) Karimian, E.; Akhlaghinia, B.; Ghodsinia, S. S. E. An Efficient and Convenient Synthesis of N-Substituted Amides under Heterogeneous Condition Using Al (HSO4) 3 via Ritter Reaction. *J. Chem. Sci.* **2016**, *128* (3), 429–439.
(24) Anxionnat, B.; Guérinot, A.; Reymond, S.; Cossy, J. $FeCl_3$-Catalyzed Ritter Reaction. Synthesis of Amides. *Tetrahedron Lett.* **2009**, *50* (26), 3470–3473.
(25) Chen, H. G.; Goel, O. P.; Kesten, S.; Knobelsdorf, J. A Novel Modification of the Ritter Reaction Using Trimethylsilyl Cyanide. *Tetrahedron Lett.* **1996**, *37* (45), 8129–8132.
(26) Yamato, T.; Hu, J.; Shinoda, N. Perflourinated Sulfonic Acid (Nafion-H) catalyzed Ritter Reaction of Benzyl Alcohols. *J. Chem. Res*. **2007**, 2007 (11), 641–643.
(27) Olah, G. A. My Search for Carbocations and Their Role in Chemistry (Nobel Lecture). *Angew. Chemie Int. Ed. English* **1995**, *34* (13-14), 1393–1405.
(28) Brandt, J. C.; Elmore, S. C.; Robinson, R. I.; Wirth, T. Safe and Efficient Ritter Reactions in Flow. *Synlett* **2010**, *2010* (20), 3099–3103.
(29) Johannsen, M.; Jørgensen, K. A. Allylic Amination. *Chem. Rev.* **1998**, *98* (4), 1689–1708.
(30) Top, S.; Jaouen, G. N-Alkylation of Nitriles Using Chromium Tricarbonyl Complexes of Benzyl Alcohol and Its Derivatives: New Perspectives for the Ritter Reaction. *J. Org. Chem.* **1981**, *46* (1), 78–82.
(31) Khaksar, S.; Fattahi, E.; Fattahi, E. Organocatalytic Synthesis of Amides from Nitriles via the Ritter Reaction. *Tetrahedron Lett.* **2011**, *52* (45), 5943–5946.
(32) Sanz, R.; Martínez, A.; Guilarte, V.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. The Ritter Reaction under Truly Catalytic Brønsted Acid Conditions. *European J. Org. Chem.* **2007**, *2007* (28), 4642–4645.
(33) D. H. R. Barton, P. D. Magnus, J. A. Garbarino, R. N. Young, *J. Chem. Soc. Perkin Trans. 1* **1974**, 2101–2107.
(34) A. García Martínez, R. Martínez Álvarez, E. Teso Vilar, A. García Fraile, M. Hanack, L. R. Subramanian, *Tetrahedron Lett.* **1989**, *30*, 581–582.
(35) M. Mukhopadhyay, M. M. Reddy, G. C. Maikap, J. Iqbal, *J. Org. Chem.* **1995**, *60*, 2670–2676
(36) Firouzabadi, H.; Sardarian, A. R.; Badparva, H.; *Synth. Commun*,**1997**, *27*, 2403-2406.
(37) Baum, J. C.; Milne, J. E.; Murry, J. A.; Thiel, O. R. An Efficient and Scalable Ritter Reaction for the Synthesis of Tert-Butyl Amides. *J. Org. Chem.* **2009**, *74* (5), 2207–2209.
(38) Nasr-Esfahani, M.; Montazerozohori, M.; Karami, Z. Efficient and green Ritter Reaction for the Synthesis of N-(t-Butyl)-and N-benzylamide from t-Butyl and Benzyl Acetate. *Org. Prep. Proced. Int.* **2016**, *48* (4), 321-327.
(39) Poon, K. W. C.; House, S. E.; Dudley, G. B. A Bench-Stable Organic Salt for the Benzylation of Alcohols. *Synlett* **2005,** *20*, 3142-3144.
(40) Poon, K. W. C.; Dudley. G. B. Heat and Mix Benzylation of Alcohols Using a Bench-Stable Pyridinium Salt. *J. Org. Chem*, **2006**, *71*, 3923-3927
(41) Poon, K. W. C.; Albiniak, P. A.; Dudley, G. B. Protection of Alcohols Using 2-Benzyloxy-1-methylpyridiniuim trifluoromethanesulfonate: methyl (R)-(-)-3-benzyloxy-2-methyl-propanoate. *Org. Synth.* **2007,** *84*, 295-305.
(42) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

(43) Novosjolova, I. The Mukaiyama Reagent: An Efficient Condensation Agent**.** *Synlett.*, **2013**, *24* (1), 135-136.
(44) Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. Synthesis of Benzyl Esters Using 2-Benzyloxy-1-methylpyridinium Triflate. *J. Org. Chem.* **2007**, *72* (23), 8962-8964.
(45) Salvati, A.; Hubley, C.; and Albiniak, P. A. Acid-and isobutylene-free synthesis of t-butyl ethers by in situ formation of 2-t-butoxy-1-methylpyridinium triflate. *Tetrahedron Lett.* **2014**, *55* (51): 7133-7135.

CHAPTER 2: SYNTHESIS OF *N*-BENZYL AMIDES

The formation of benzyl ethers[1,2] and benzyl esters[3] was successfully optimized using 2-benzyloxy-1-methylpyridinium triflate (BnOPT) **(1.134)** as a benzyl transfer agent. The proposed mechanism of benzyl transfer using BnOPT **(1.134)** involves an S_N1-like pathway where BnOPT decomposes to a benzyl cation upon warming followed by trapping with the respective nucleophile. If this mechanism is correct, benzyl transfer *via* BnOPT should be possible with any nucleophile of choice. The efficiency of BnOPT in reaction with alcohols and carboxylic acid, shifted our focus toward transferring benzyl groups to other nucleophiles like nitriles. Since nitriles are weaker nucleophiles than alcohols and activated carboxylic acids, they could be more challenging targets for reactions with BnOPT. This chapter will focus on the investigation of the reactivity of nitriles with oxypyridinium salts resulting in *N*-benzyl amide formation. This useful conversion of nitriles to amides was first described by J. J. Ritter in the late 1940's.[4] Traditional Ritter reactions typically involve strongly acidic conditions to generate the carbocation and the subsequent reaction with nitrile to form nitrilium ion which yield the amide via hydrolysis, while BnOPT would allow for much milder conditions. As shown in **Scheme 2.1**, and based on proposed mechanism, BnOPT **(1.134)** decomposed upon warming and nucleophilic attack of a nitrile **(2.1)** resulted in formation of an intermediate ion **(2.2).** Resultant nitrilium ion **(2.2)** was then quenched with water in order to generate an *N*-benzyl amide **(2.3)**. The driving force for this reaction is the neutralization of the positive charge on the pre-activated nitrogen of **(1.134)**.

Scheme 2.1: Proposed Mechanism for Amide Synthesis Using BnOPT

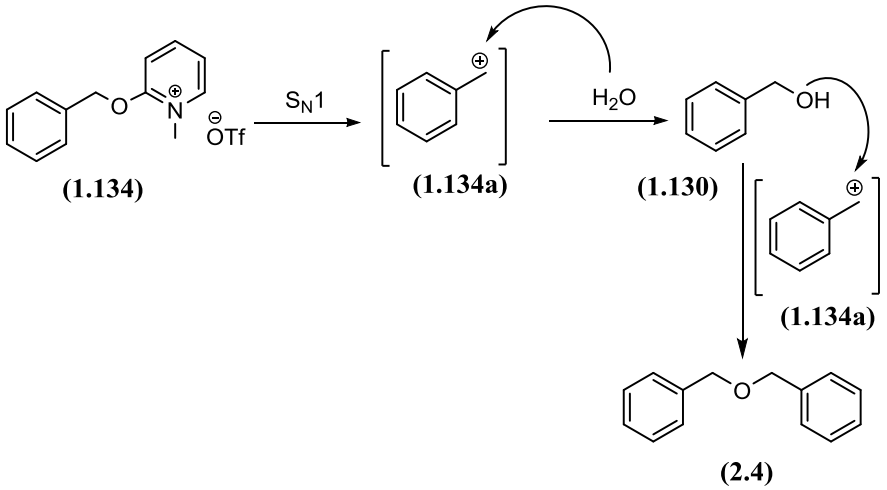


2.1 Initial Attempt for *N*-Benzyl Amide Synthesis using BnOPT

The first objective was to synthesize BnOPT **(1.134)** by mixing 2-chloropyridine **(1.131)**, 18-crown-6 and the potassium salt of benzyl alcohol **(1.130)** in refluxing toluene for an hour under an argon atmosphere. 2-Benzyloxypyridine **(1.132)** was subsequently alkylated using methyl triflate **(1.133)** to form 2-Benzyloxy-1-methylpyridinium triflate **(1.134) (Scheme 1.29)**.[5] The best methylation protocol is dropwise addition of methyl triflate to an ice-cold solution of **(1.132)** in toluene over the course of ten minutes. Then the reaction mixture was allowed to warm to room temperature. In the last step, the mixture was stirred for an hour under an argon atmosphere. The triflate salt precipitates from the reaction mixture as a white, crystalline that is stable to storage at room temperature. Alternatively, BnOPT is now commercially available from Sigma Aldrich.[6] The second step was to explore reactions of BnOPT in presence of nitriles. Initial attempts used identical conditions as the reaction of BnOPT with alcohols and carboxylic acids. Therefore, BnOPT **(1.134)** was dissolved in the mixture of a nitrile in trifluorotoluene at 83 °C for 24h under an argon atmosphere. Initial screening with benzonitrile and benzyl cyanide as the nitriles proved that the reaction is viable, but the crude sample spectra indicated poor conversion of nitrile to amide (12-20% conversion). Also, during *N*-benzyl amide synthesis, a side reaction resulted in formation of dibenzyl ether **(2.4)** as an unwanted byproduct. The formation of dibenzyl ether as a

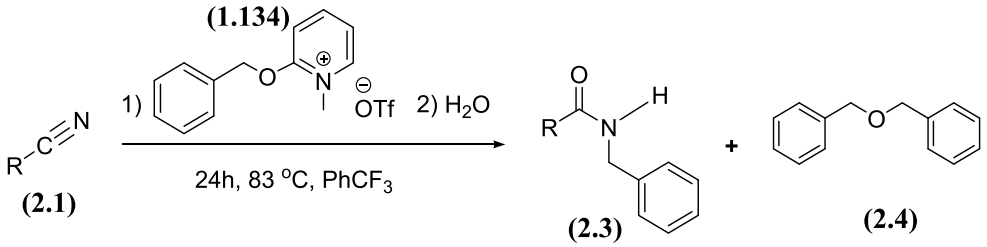
byproduct was not unexpected in the reaction of BnOPT with nitriles under these conditions, since BnOPT reactions are susceptible to a side reaction in the presence of any trace amount of water. The hypothesis was that the interference from water is due to the direct attack of this molecule (from adventitious moisture or the water which is used in quenching step) as the nucleophile to the benzyl carbocation **(1.134a)** which results in formation of benzyl alcohol **(1.130)**. This benzyl alcohol **(1.130)** reacts as the dominant nucleophile in the second step and leading to the formation of dibenzyl ether **(2.4)** as an unwanted and competitive byproduct **(Scheme 2.2)**.[7]

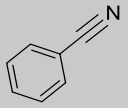
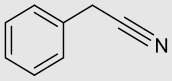
Scheme 2.2: Formation of Dibenzyl Ether Byproduct



For complex molecules trace amounts of dibenzyl ether should not be a concern; However, it was a competitive byproduct for *N*-benzyl amide synthesis during initial attempt with nitriles.

Table 2.1: Initial Results of *N*-Benzyl Amide Synthesis Using BnOPT



2.1	Substrate	2.3:2.1 ratio	2.3:2.4 ratio	Crude Recovery(%)
a		1:4	3.4:1	102
b		1:7	1.6:1	90

Although the reaction of nitriles with BnOPT proceeded toward *N*-benzyl amide synthesis, the formation of dibenzyl ether in high ratios was a major problem during initial attempts as shown in Figure 2.1.

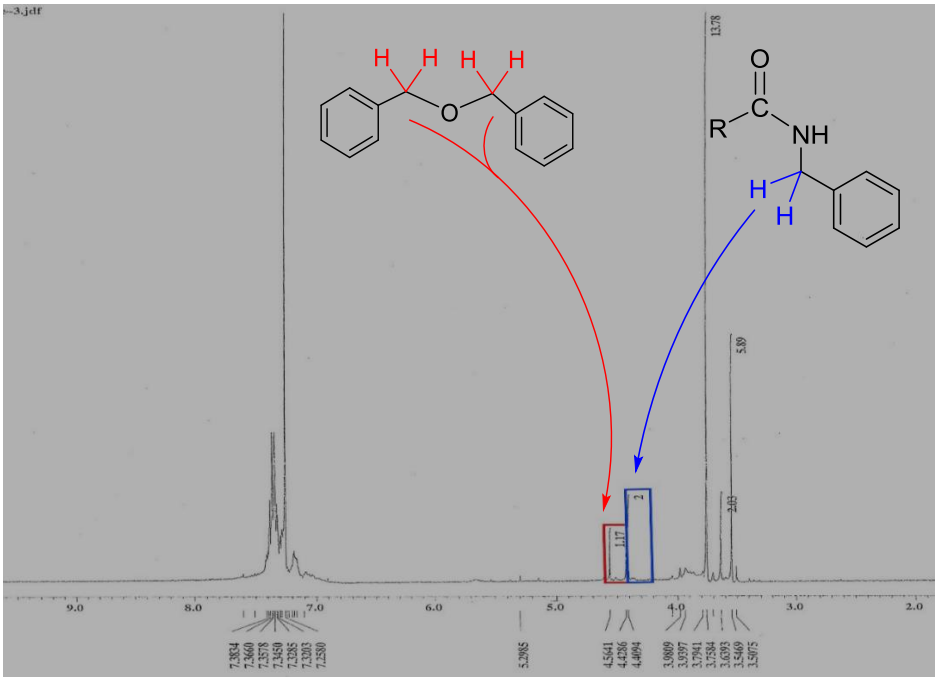


Figure 2.1: Formation of Competetive Byproduct Using BnOPT for Amide Synthesis

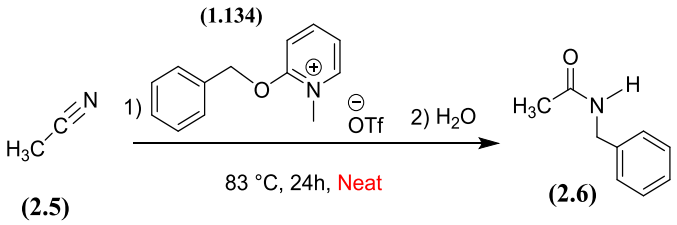
Several experiments were performed to see if we obtained the same ratios of dibenzyl ether using different nitrile compounds under the same conditions. The formation of same byproduct molecule during almost all of the experiments when trifluorotoluene was used as the solvent led to investigate this reaction in presence of other solvents to check if solubility of the salt could be an issue for reaction progress.

2.2 *N*-Benzyl Amide Synthesis Using BnOPT Under Neat Conditions

In the search for other solvents which could be used in efficient conversion of nitriles to benzyl amides, the main focus was to look for a polar aprotic solvent to stabilize the proposed highly polar transition state. Previous studies with BnOPT revealed that aromatic solvents, in which BnOPT dissolves upon warming, were better suited for efficient benzylation, even though highly polar aprotic solvents more expected to be beneficial. Theoretically, polar protic solvents could be helpful in stabilizing the transition state but they could also interfere in the reaction as nucleophiles. Therefore, a series of polar aprotic solvents were selected to test their ability in order to promote the synthesis of *N*-benzyl amide in the absence of any competitive byproduct. Acetonitrile was the first solvent that was selected based on its desirable characteristics. First of all, acetonitrile has a cyano group in its structure which could push equilibrium towards product synthesis. Moreover, it is one of the most common polar aprotic solvents that could be used in S_N1 reactions. Additionally, when acetonitrile is used in reaction with BnOPT, it plays a dual role, both as a solvent and a nucleophile.[8] In the early stage of screening, BnOPT **(1.134)** was dissolved in acetonitrile **(2.5)** as the solvent of reaction and the mixture was heated at 83 °C until the completion of reaction which was monitored via TLC. The reaction mixture was then quenched with water

and was allowed to stir for 1h at room temperature. ^{1}H NMR was used to determine the ratios of product to starting material. Based on ^{1}H NMR spectra, no dibenzyl ether was formed during this reaction under neat conditions. Higher yield of **(2.6)** (58% in 3:2 equiv of acetonitrile:salt, and 88% in 2:1 equiv of acetonitrile:salt), compared to the initial attempt was another advantage of this new condition. Based on NMR analysis, complete conversion of acetonitrile to *N*-benzyl acetamide **(2.6)** occured during this reaction.

Scheme 2.3: *N*-Benzylacetamide Synthesis in Presence of Acetonitrile



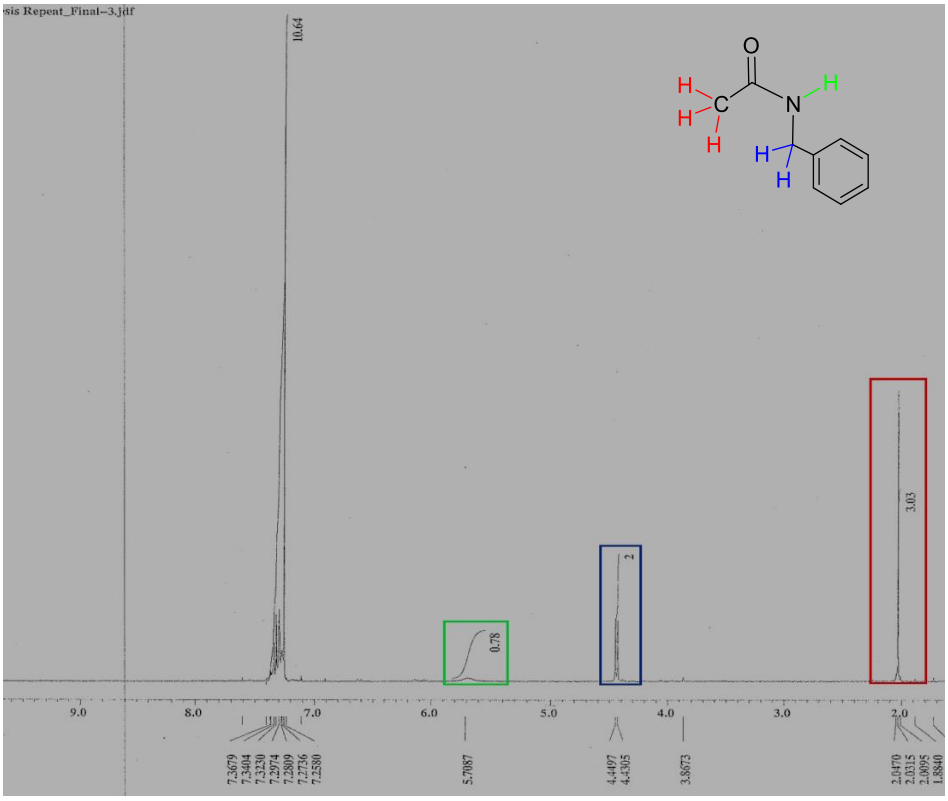


Figure 2.2: *N*-Benzylacetamide Formation Under Neat Conditions

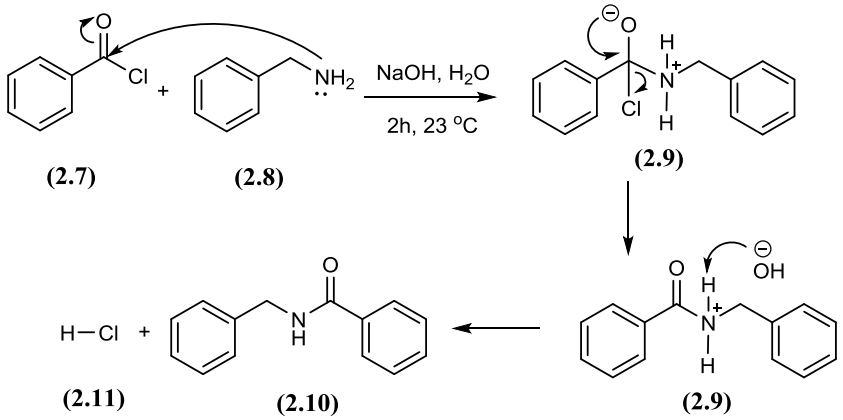
After successful synthesis of *N*-benzylacetamide **(2.6)** from the reaction of acetonitrile **(2.5)** and BnOPT **(1.134)** under neat conditions, the focus shifted toward selecting neat conditions for other *N*-benzyl amide formations. Traditionally, the drive for the development of solvent-less/neat reaction consists of: economics (save money on solvents), ease of purification (no solvent removal post-synthesis), high reaction rate (due to high concentration of reactants), and environmentally friendly condition (solvent is not required).[9] To investigate whether this method could be generally applicable for the conversion of nitriles to amides using BnOPT, benzonitrile and benzyl cyanide were selected for testing under neat condition for the formation of *N*-benzylbenzamide and *N*-benzyl-2-phenylacetamide, respectively. Before we started to investigate the reactivity of BnOPT in transferring a benzyl group to the selected nitriles under neat conditions, a classical known method for *N*-benzylbenzamide synthesis was selected with the aim of having a standard method to compare the resultant amide, the Schotten-Baumann procedure. In this procedure the formation of *N*-benzylbenzamide **(2.10)** was accomplished by mixing benzoyl chloride **(2.7)** and benzylamine **(2.8)** in presence of a large amount of base in solution to absorb the acid **(2.11)** that is produced.[8] The Schotten-Baumann procedure for *N*-benzylbenzamide can be achieved under three different reaction conditions:[10]

1. THF (solvent) / TEA (base): This procedure was outlined in Cho *et al*.[11] While this reaction was successful, the flammability of THF prevented this method from being useful and safe condition.

2. H_2O (solvent) / NaOH (base): This procedure was adapted from the amine synthesis described by Marvel *et al*.[12] Although a competing reaction occurred between benzoyl chloride and water, this ultimately proved most successful with respect to safety and simplicity, even though it produced lower yields than the THF/TEA reaction.

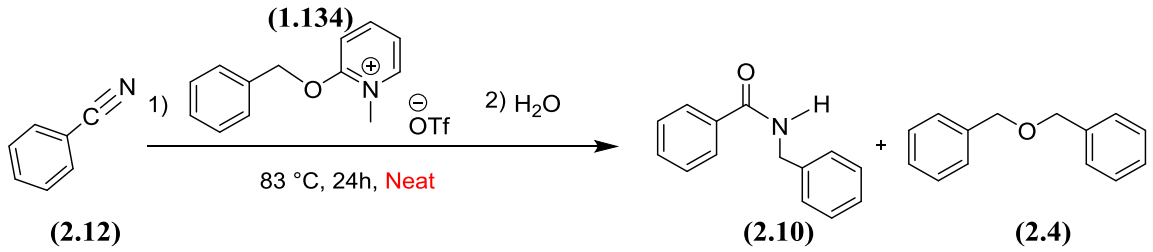
3. H_2O (solvent) / SDS: This procedure was adapted from Naik *et al.*[13] and used H_2O as the solvent and sodium dodecyl sulfate (SDS) as the phase transfer catalyst. While this procedure was a desirable alternative to the use of strong bases as an example of environmentally friendly chemistry, the desired product proved difficult to separate from the SDS. Availability and simplicity of reagents were considered to choose an ideal solvent/base combination for this purpose. Therefore, the synthesis of *N*-benzylbenzamide **(2.10)** was carried out in water. The optimal ratios were determined to be 1:1:3 of benzoyl chloride **(2.7)** to benzylamine **(2.8)** to NaOH. In this reaction, benzoyl chloride is added during the course of 1h and the reaction is cooled by running water **(Scheme 2.4)**.

Scheme 2.4: *N*-Benzylbenzamide Synthesis Using Schotten-Baumann Reaction



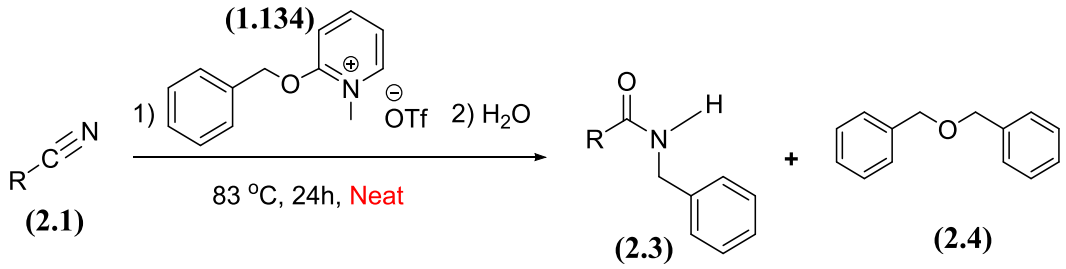
The desired product was recrystallized using hexane/ethyl acetate to afford *N*-benzylbenzamide **(2.10)**. With **(2.10)** in hand, the capability of BnOPT for the formation of same product was investigated. This time *N*-benzylbenzamide **(2.10)** was synthesized by stirring BnOPT **(1.134)** in benzonitrile. The reaction mixture was allowed to stir at reflux (83 °C) for 24h under an argon atmosphere, then quenched with water. The result was the formation of *N*-benzylbenzamide **(2.10)** and small amounts of byproduct (<15%), dibenzyl ether **(2.4)**.

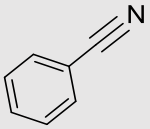
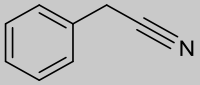
Scheme 2.5: *N*-Benzylbenzamide Synthesis Using BnOPT Under Neat Condition



^{1}H NMR was used to determine the ratios of amide to nitrile **(2.10:2.12)** and the ratio of amide to dibenzyl ether **(2.10:2.4)**. These ratios were obtained by comparing the integration of the benzylic hydrogens of the amide and the dibenzyl ether. After the crude sample was purified and *N*-benzylbenzamide was separated from byproduct, it was compared with the standard amide product that was obtained earlier using Schotten-Baumann reaction. Hydrogen peaks in the ^{1}H NMR spectrum supported the formation of the desired product using BnOPT under neat conditions as shown in Figure 2.3. Since the reaction of both acetonitrile and benzonitrile with BnOPT reached completion with isolated yields in the range of 60-98%, the same reaction was applied to benzyl cyanide to evaluate the applicability of this method for benzyl transfer to benzyl cyanide in order to generate the corresponding benzyl amide. Benzyl cyanide **(2.1c)** was also added to BnOPT **(1.134)** under neat condition. The reaction mixture was placed in the oil bath and stirred at 83 °C for 24h. Again ^{1}H NMR spectroscopy was used to investigate the completion of reaction and the probability of any side reaction occurrence. As expected from previous reaction with benzonitrile, dibenzyl ether **(2.4)** was formed as a byproduct, but unlike the previous reactions the amount of byproduct was comparable to the amide product **(2.3c)**. This substrate was also more challenging with respect to the completion of the reaction. As shown in Table 2.2, the reaction was not complete after 24h.

Table 2.2: Efficiency of *N*-Benzyl Amide Synthesis Using BnOPT Under Neat Condition



Entry	Substrate	(2.3:2.1) ratio	(2.3:2.4) ratio	Yield(%)
a		>99:1	>99:1	88
b		>99:1*	2.7:1	71
c		>1:5	1:8	54

* To measure the ratio of amide to the nitrile the ratio of integrations in ^{1}H NMR was considered. In the benzonitrile example the reaction was presumed complete based on clean spectra and high yield. However, it is possible that excess amounts of benzonitrile was left in the reaction flask, since the reaction was setup at 3:2 equiv of nitrile:salt.

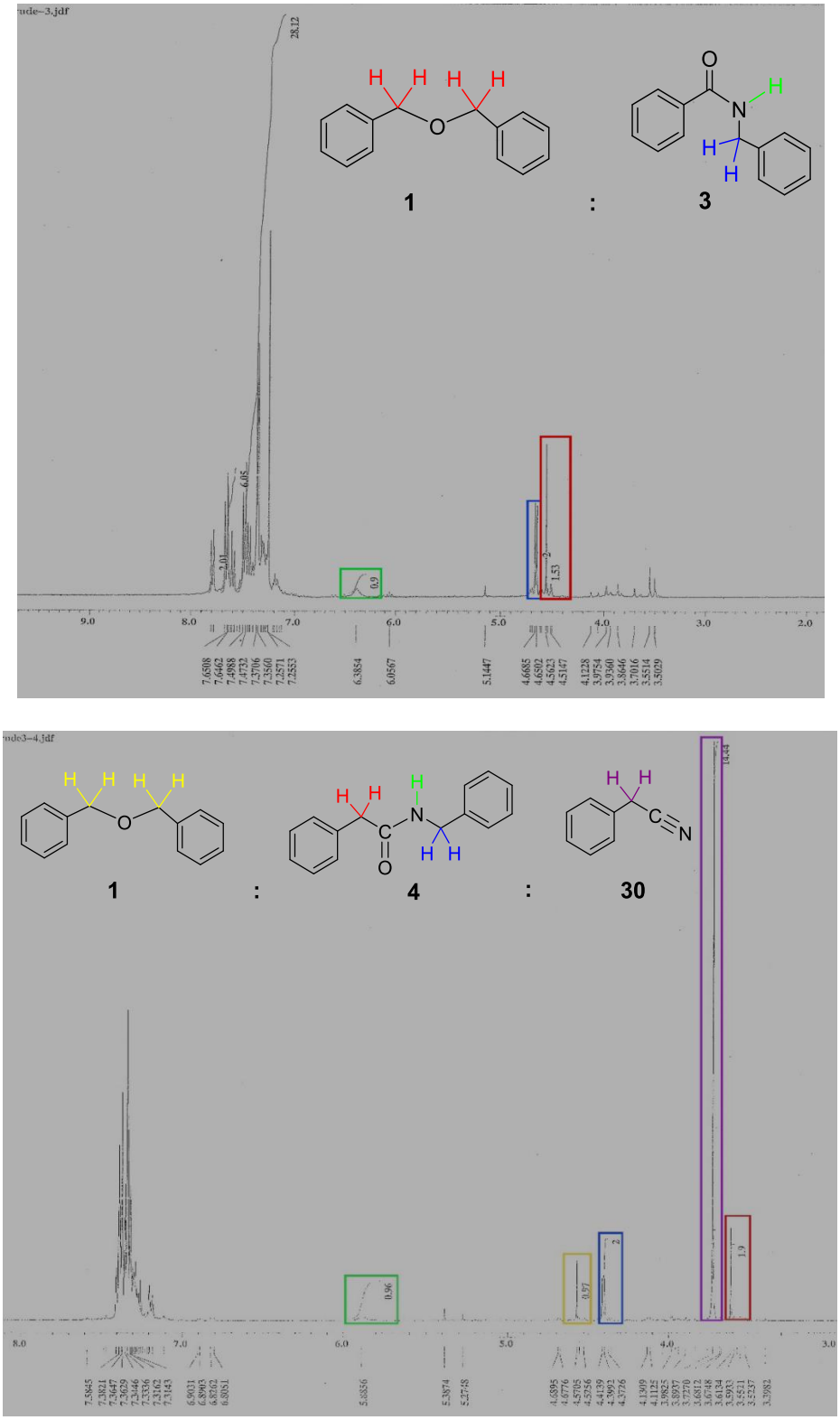


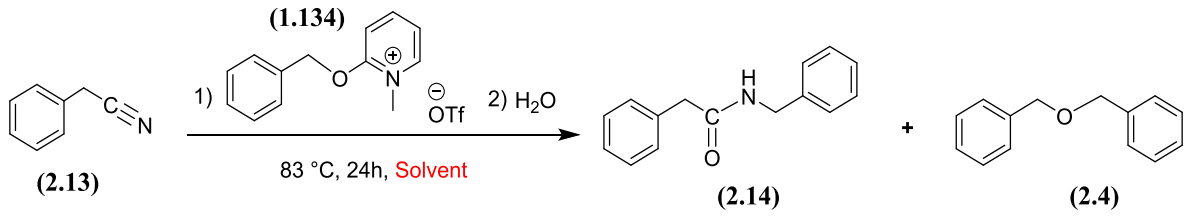
Figure 2.3: ^{1}H NMR of a) *N*-Benzylbenzamide b) *N*-Benzyl-2-phenylamide (Crude Mixture)

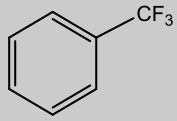
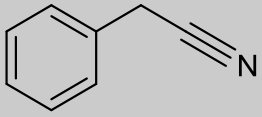
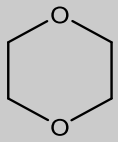
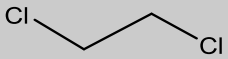
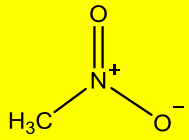
Successful conversion of nitriles to amides (in moderate to high yields) under neat condition supported the idea that BnOPT could transfer benzyl groups even to relatively weak nucleophiles. However, since nitriles in these reactions were used in excess amounts (in order to play a dual role), there is a concern of wasting substrates. Moreover, neat conditions are not the best choice when large or expensive nitriles with higher boiling points are targeted. The promising positive results of neat condition along with its limitations led us to pursue an investigation of other variables in order to develop much more efficient benzyl transfer reaction.

2.3 Screening the Effect of Solvents and Other Variables in the Reaction of Nitriles with BnOPT

After investigating the reaction of nitriles under neat conditions, this reaction was then screened with different solvents. BnOPT reactions have favored aromatic solvents in previous studies, even though theory predicts polar aprotic solvents to be beneficial. To compare the effect of aromatic solvents, neat condition and polar aprotic solvents, the reaction of benzyl cyanide and BnOPT was investigated in presence of these solvents. This screening also investigated different times and temperatures. To evaluate the effect of each solvent in promotion of such a reaction using BnOPT, the ratios of *N*-benzyl-2-phenylacetamide **(2.14)** to benzyl cyanide **(2.13)** and of benzyl cyanide **(2.13)** to dibenzyl ether **(2.4)** were determined using integration of benzylic hydrogens in the ^{1}H NMR spectrum.

Table 2.3: Solvent Screening for *N*-Benzyl Amide Synthesis



Solvent	Entry	Time (h)	Temperature (°C)	2.14:2.13	2.14:2.4
	1	24	83	1:5	1:2.3
	2	48	83	1:9	1:1.5
	3	24	83	1:3.5	50:1
	4		110	1:5.8	>99:1
	5	48	83	1:4	>99:1
	6		110	1:5	>99:1
	7	24	83	1:6	1:1
	8		110	1:8	1:1.2
	9	48	83	1:7.3	1:1
	10		110	1:6.6	1:1
	11	24	83	1:4.5	33.1
	12		110	1:5.6	11.1
	13	48	83	1:5.2	16.1
	14		110	1:7.3	18.1
	**15**	**24**	**83**	**1:2.5**	**>99:1**
	16		110	1:4	50:1
	17	48	83	1:2.5	6:1
	18		110	1:3	3:1

Benzyl cyanide **(2.13)** and 2-benzyloxy-1-methylpyridinium triflate **(1.134)**, were dissolved in each solvent screened and the reaction mixture was heated at (83 or 110 °C). Each reaction was monitored both after 24h and 48h to compare the effect of time in reaction completion and byproduct formation. In most cases a mixture of benzyl amide **(2.14)** and dibenzyl ether **(2.4)** was observed in ^{1}H NMR for the crude mixture. As shown in Table 2.3, in presence of trifluorotoluene

(entries 1-2), dichloroethane, and dioxane (entries 7-14), majority of benzyl cyanide remained after the 24h. Surprisingly, in some of these reactions the conversion was much weaker after 48h (entries 2,8,12, and 14), which could be explained by more decomposition of corresponding nitrilium intermediate before quenching with water or by decomposition or further reactions of products. Dibenzyl ether formation was also observed in large amounts with these three solvents (entries 7-14). Trifluorotoluene was the aromatic solvent that showed the best results in the reaction of BnOPT with alcohols and carboxylic acids, but in this case, it yielded poor results. Benzyl cyanide formed very little dibenzyl ether after 48h under neat condition (entry 5,6). However, these conditions were dismissed due to very low conversions (16-20%). When nitromethane was used, the reaction showed much higher conversion after 48h (entry 17,18), but a relatively larger amounts of dibenzyl ether was being formed as well (8-16%). Ultimately, nitromethane after 24h at 83 °C proved to be the most effective solvent for facilitating consumption of benzyl cyanide, as it led to the fastest reaction times and less byproduct formation (entry 15). The results of this screening revealed that solubility of salt in reaction mixture and also stability of nitrilium intermediate should be considered as potential concern regarding these types of reactions. However, even under the most favorable solvent conditions, shorter time duration of reaction was favored, which might indicate stability of intermediate and products is an important factor in this reaction. The latter effect was shown in Figure 2.4**.**

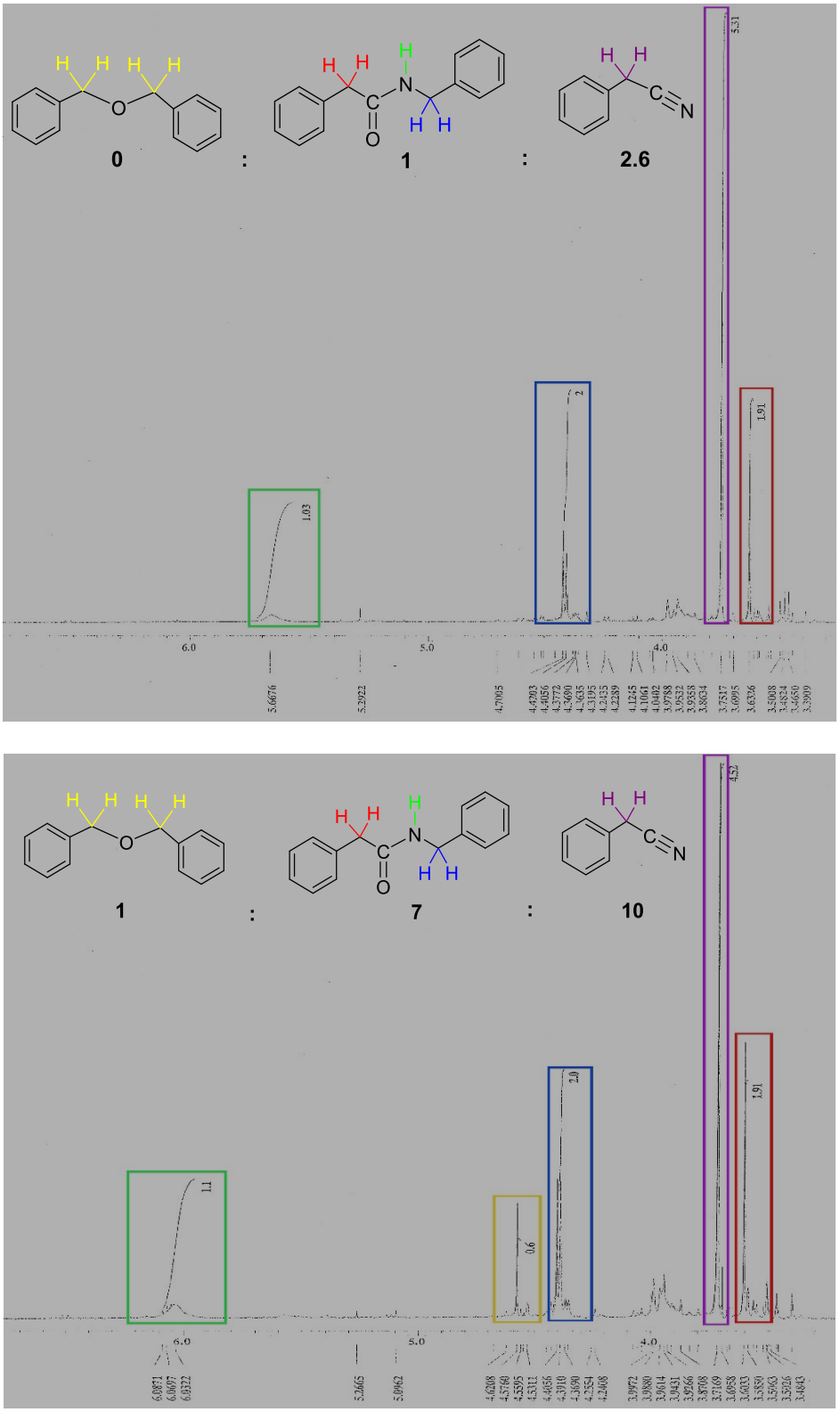


Figure 2.4: *N*-Benzyl-2-phenylacetamide Synthesis After a) 24 h at 83 °C, b) 48 h at 83 °C

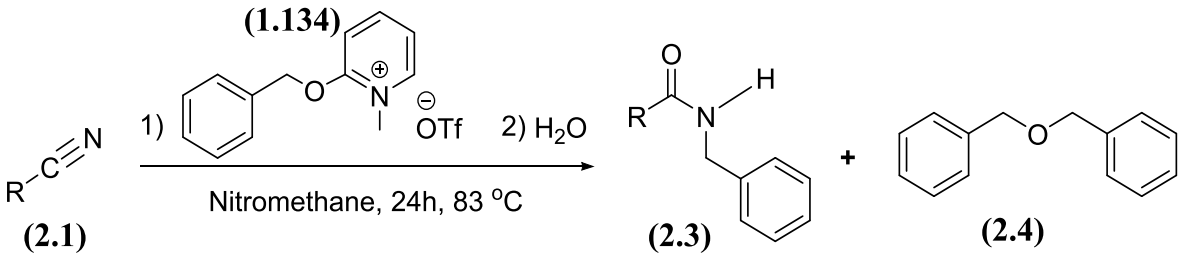
As shown in Figure 2.4, when nitromethane was used as the solvent, no dibenzyl ether was formed after 24h, even though as the reaction proceeded, more dibenzy ether was formed during the course of reaction. Additionally, in this case the conversion ratio remained the same after 24 and 48h.

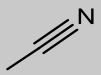
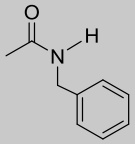
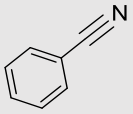
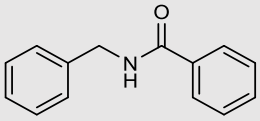
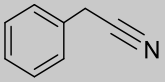
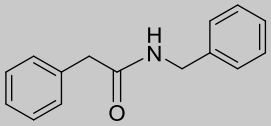
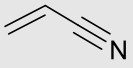
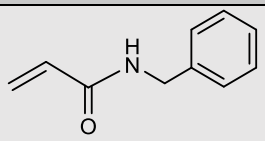
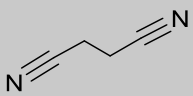
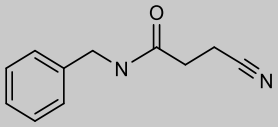
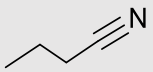
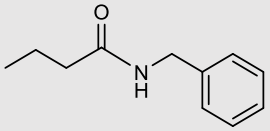
2.4 Substrate Screening of Nitriles

Based on results of previous section, nitromethane was the best solvent for benzyl cyanide conversion, even though the results of this solvent conditions were still not great. Therefore, to investigate how nitromethane works in reaction with other nitriles and in order to evaluate if these conditions were universally mediocre or if the benzyl cyanide was a poor substrate in earlier tests, other nitriles were studied in reaction under the nitromethane conditions. Nitriles were selected in this substrate screening based on either their previous positive results under neat conditions or promising results in the traditional Ritter reaction. BnOPT **(1.134)** was dissolved in nitromethane for each nitrile screened and the reaction mixture was heated up to 90 °C. Each reaction was monitored after 4, 8, 12 and 24h to have a better idea of reaction progression during the course of reaction. As shown in Table 2.4, in all the entries except acrylonitrile, a mixture of both expected *N*-benzyl amide **(2.3)** and dibenzyl ether **(2.4)** were formed. The results of acetonitrile **(2.1a)** and benzonitrile **(2.1b)** reactions were promising with relatively high conversion rate (>50%) and low dibenzyl ether formation. Succinonitrile **(2.1e)** was another nitrile that was studied in substrate screening. This nitrile seemed to be a desirable starting material due to the presence of two cyano groups in its structure; However, experimental data showed a larger amount of dibenzyl ether formation in the reaction of this nitrile with BnOPT compared to acetonitrile **(2.1a)** and benzonitrile **(2.1b)** results. Additionally, the reaction of butyronitrile **(2.1f)** and BnOPT led to the formation of both *N*-benzylamide **(2.3)** and the dibenzyl ether **(2.4)**. Although the incomplete

consumption of butyronitrile was observed in this screened reaction, it was more effective with respect to the less formation of undesired byproduct.

Table 2.4: Substrate Screening of Nitriles in *N*-Benzyl Amide Synthesis Using BnOPT

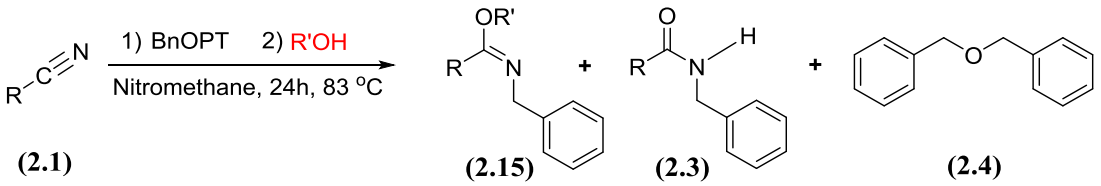


2.1	Substrate	2.3	Product	2.3:2.1	2.3:2.4
a		**a**		> 99:1	> 99:1
b		**b**		1.5:1	10:1
c		**c**		1:2.5	> 99:1
d		**d**		-	-
e		**e**		1:5	15:1
f		**f**		1:4	25:1

Ultimately, the reaction of acrylonitrile **(2.1f)** was screened under the same conditions. This nitrile **(2.1f)** was consumed completely during the reaction time even though there was no sign of amide synthesis. The conjugated system in the structure of acrylonitrile might be the reason for this result in reaction with BnOPT. In fact, this nitrile is a potential candidate for other reaction mechanism such as addition polymerization. To test this hypothesis, further experiments should be carried out in the future. As substrate screening showed, most substrate experienced less than 50% conversion which could suggests that the reaction has some S_N2-like characteristics with the nucleophile being involved in the rate-determining step. Since nitriles are weaker nucleophiles compared to alcohols and activated carboxylic acids, benzyl transfer to these substrates are less efficient if S_N2-type of reaction. Additionally, the solubility of salt and the instability of nitrilium intermediate could be other potential problems with this reaction. In order to check if the weak nucleophilicity of nitriles is the main issue of such reactions and with the aim to have a better idea of the true source of water involving in the formation of dibenzyl ether, several changes were made in quenching step. It is good to note that although the water was known responsible for dibenzyl ether formation in BnOPT reactions, it was not proved if this water comes from the quenching step or if it is from the adventitious moisture. Therefore, in order to eliminate any possibilities of nucleophilic competition between water and nitrile in quenching step, dried alcohols were used instead of water for rinsing the reaction. It was expected to get no dibenzyl ether formation if there was no water interference before quenching with alcohol. In other words, in the absence of water, a majority of benzyl cation would be attacked by nitrile to form the nitrilium ion and there is no chance of getting dibenzyl ether. Alternatively, if dibenzyl ether was formed under this new reaction conditions, it was concluded that there were some water molecules around in the flask or in the salt crystals that

could compete with nitrile in order to attack the benzyl cation before quenching step. To test each of these possibilities, different reactions were setup using benzyl cyanide under the same conditions as before. After 24h at 83 °C the reactions were quenched with different alcohols.

Scheme 2.6: Potential Sources of Water Responsible for Dibenzyl Ether Formation

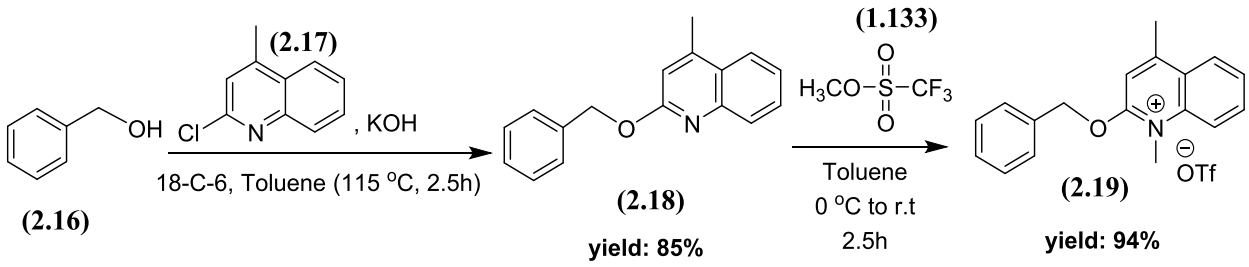


1-propanol proved to be the most effective alcohol for quenching. The excess amount of this alcohol was easily removed after workup. This study has shown that a combination of products can be made when alcohol was used for quenching the reaction. The formation of dibenzyl ether **(2.4)** was a proof of presenting water in the flask even before the reaction was quenched with alcohol. On the other hand, dibenzyl ether **(2.4)** was not the only product that was formed during this study which is a sign of nitrile ability in the nucleophilic competition with water. In fact, at least some of the nitrile molecules were able to attack the benzyl cation in order to form the nitrilium intermediate and subsequently **(2.15)**. Additionally, the formation of both **(2.15)** and **(2.3)** can be used as a proof of stability of nitrilium intermediate until the quenching step using alcohol. Therefore, the results of this study has shown that the weak nucleophilicity of the nitrile cannot be the main issue in the reaction of these compounds with BnOPT. Moreover, the instability of nitrilium might not prevent the reaction from *N*-benzylamide synthesis.

2.5 Using Other Oxypyridinium Salts as Benzyl Transfer Reagents

The success of 2-benzyloxy-1-methylpyridinium triflate as a reagent for benzylating some of the nitrile derivatives was encouraging; However, its limitation for complete conversion of other nitriles like succinonitrile, butyronitrile and acrylonitrile led us to investigate the reactivity of other oxypyridinium salts. In fact, the next goal was to study the effect of different precursors to oxypyridinium salt. 2-Benzyloxy-1-methyllepidinium triflate was one of oxypyridinium salts that was screened in regards to its ability to transfer benzyl group to nitrile derivatives. This reagent was presumed to work better compared to BnOPT, since it is more soluble analog of BnOPT. Moreover, this salt contains an additional aromatic ring which could stabilize the electron density through resonance once decomposed to cation/anion pair. The more stable resultant cation/anion pair is due to the enhanced reactivity of this salt compared to BnOPT. The reagent 2-benzyloxylepidine **(2.18)** was synthesized by mixing benzyl alcohol **(2.16)** with 2-chlorolepidine **(2.17)**, and potassium hydroxide. The reaction mixture was allowed to stir at reflux (115 °C) for 2.5 hours under an argon atmosphere **(Scheme 2.7)**. This precursor is an analogous to 2-benzyloxypyridine.

Scheme 2.7: Synthesis of 2-benzyloxy-1-methyllepidinium triflate (BnOLT)

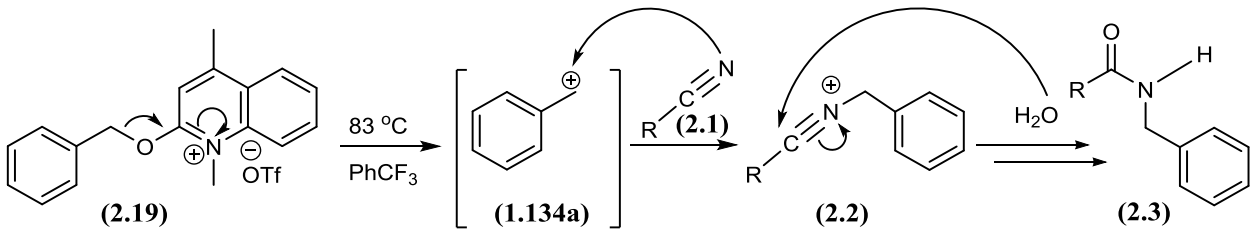


2-Benzyloxylepidine **(2.18)** was dissolved in toluene and cooled to 0 °C in an ice bath and then methyl triflate **(1.133)** was added dropwise over the course of ten minutes. The reaction mixture was allowed to warm to room temperature and stir under an argon atmosphere for two hours. Preliminary experiments showed that unlike BnOPT, the lepidine derivative is much more soluble

in aromatic solvents; Therefore, the addition of methyl triflate (MeOTf) **(1.133)** to 2-benzyloxylepidine **(2.18)** in trifluorotoluene did not result in rapid salt precipitation. However, TLC analysis proved consumption of 2-benzyloxylepidine **(2.18)** with concomitant formation of 2-benzyloxy-1-methyllepidinium triflate (BnOLT) **(2.19)** salt after 2.5h. Similar to BnOPT, BnOLT **(2.19)** is a bench stable salt which has a pre-activated nitrogen that precludes the need for strong acid or base in reaction mixture. Therefore, this lepidine salt could be a suitable candidate for benzyl transfer reagent under mild conditions.

After formation of 2-benzyloxy-1-methyllepidinium triflate **(2.19)**, a general procedure was applied to investigate the reactivity of this reagent in reaction with nitriles. First, this salt **(2.19)** was dissolved in the mixture of a nitrile **(2.1)** in trifluorotoluene at 83 °C for 24h under an argon atmosphere. As shown in Scheme 2.1, the resultant nitrilium ion **(2.2)** was then quenched with water in order to generate the corresponding *N*-benzyl amide **(2.3) (Scheme 2.8)**.

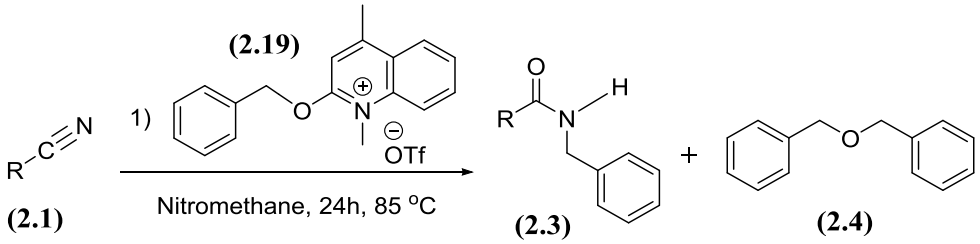
Scheme 2.8: *N*-Benzyl Amide Synthesis Using BnOLT

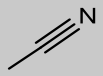
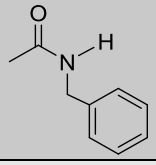
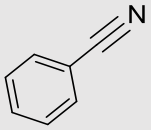
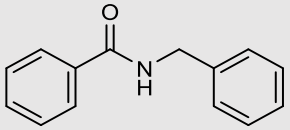
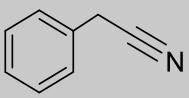
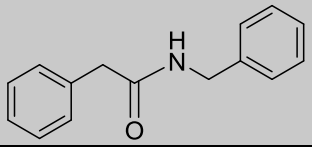


In general, the proposed mechanism of this reaction is analogous to the benzylation mechanism of BnOPT. Although, BnOLT **(2.19)** forms the same carbocation during decomposition, this salt is more soluble which could cover the solubility concern of such reactions. Additionally, there is a hypothesis that BnOLT is more reactive than BnOPT. More stable lepidine residue could assist decomposition of BnOLT salt. Therefore, this salt could serve as a stronger electrophile precursor for transferring benzyl group to weaker nucleophiles like nitriles.

Acetonitile and benzonitrile were selected based on the success that these two nitriles had showed with BnOPT. For each of them, two experiments were set up, one in trifluorotoluene and the other one in nitromethane. In all cases, a mixture of corresponding *N*-benzyl amide **(2.3)** and dibenzyl ether **(2.4)** was observed in the ^{1}H NMR spectra of crude reaction sample. However, reactions in nitromethane showed better consumption of starting material and less formation of dibenzyl ether compared to trifluorotoluene, which was consistent with the results of benzyl amide synthesis using BnOPT. In contrast to the previous expectations based on better solubility profile and enhanced stability of electrophile precursor, the substrate screening of BnOLT revealed less amide synthesis (20-25%) under the same condition compared to BnOPT (30-90%).

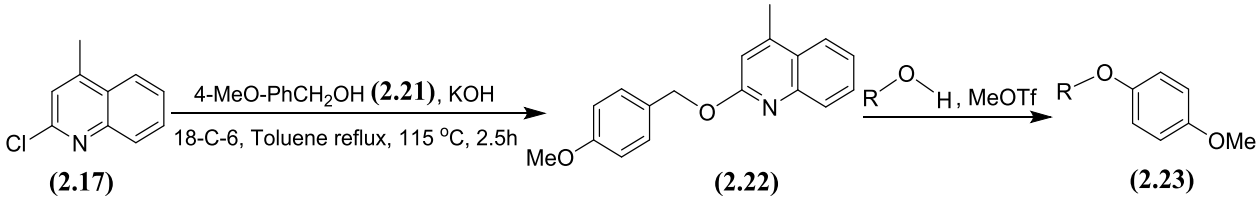
Table 2.5: Substrate Screening of Nitriles in *N*-Benzyl Amide Synthesis Using BnOLT



2.1	Substrate	2.3	Product	2.3:2.1	2.3:2.4
a		**a**		1:3	> 99:1
b		**b**		1:3	10:1
c		**c**		1:1	20:1

The results of these experiments highlights the idea that solubility is not the only concern in the reaction of nitriles with oxypyridinium salts. As shown in this substrate screening, even with enhanced solubility of precursor, it did not prompt the reactions to completion. Therefore, trying other electrophile precursors with higher reactivity was inevitable. With the poor results using BnOLT in mind, the next goal was to find a precursor that would allow easier decomposition to yield the electrophile. In the search for such precursor, alcohols were first used as model substrate in literature. Base on previous studies, *p*-methoxybenzyl (PMB) was one of the attractive groups for transferring to alcohols. PMB group is a very stable carbocation which makes it a potential candidate for the postulated S_N1 mechanism. Additionally, high stability of this carbocation is the reason for instability of corresponding salt at room temperature. Transferring this group is quite useful in synthetic chemistry. For instance, PMB ethers are workhorse protecting group in organic synthesis. Common methods for formation of PMB ethers are Williamson and trichloroacetimidate coupling reactions.[14] However, almost all of these methods require basic or acidic media that may not be compatible with complex systems. Furthermore, neither PMB trichloroacetimidate (unstable to storage) nor PMB chloride (lachrymator) is especially convenient for routine usage. Successful results with PMBOLT in literature, introduced a new way to transfer PMB group to alcohols with the aid of *p*-methoxy-2-benzyloxy-1-methyllepidyl triflate. To make this salt, a more hydrophobic reagent, 2-chlorolepidine **(2.17)**, was targeted and 2-(4- methoxybenzyloxy)-4-methylquinoline **(2.22)** was prepared.[15]

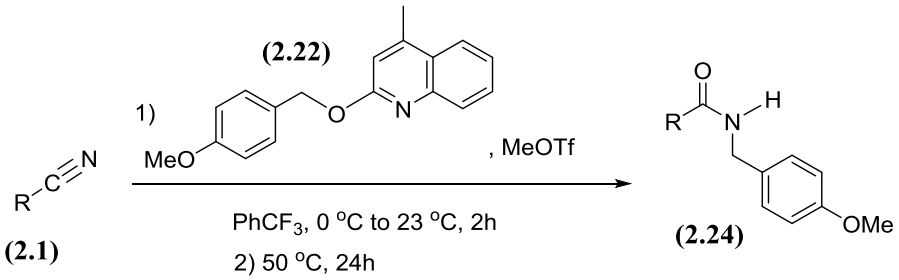
Scheme 2.9: Synthesis of 2-(4- methoxybenzyloxy)-4-methylquinoline



(2.17) **(2.22)** **(2.23)**

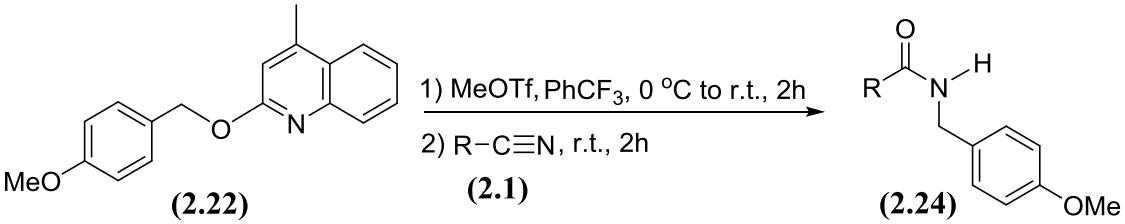
Lepidine ether **(2.22)** was then methylated using methyl trifalte significantly. To overcome the limited stability of the *para*-methoxybenzyloxylepidine (PMBO-lepidine) salt, the reagent is best generated in situ. As previously mentioned this PMB lepidine was initially tested in reaction with alcohols. An ice-cold mixture of **(2.22)**, trifluorotoluene, MgO, and alcohol was treated dropwise with methyl triflate over 20min. The ice bath was then removed, and the reaction mixture was stirred at room temperature for 30–60 min until TLC analysis showed consumption of alcohol. The product yield for alcohols was higher than 80%. To investigate the possibility of transferring PMB group to nitriles in order to form *p*-methoxybenzyl amide **(2.24)**, at first the same conditions as alcohols were used, except for the room temperature that was replaced with oil bath at 50 °C. The temperature was raised with the aim of preparing better solubility and reactivity of reagents. Additionally, MgO was not used in reaction of nitriles. A solution of a nitrile **(2.1)**, and the PMB lepidine ether **(2.22)** in $PhCF_3$ was stirred at 0 °C **(Scheme 2.10)**. MeOTf was then added dropwise, and upon complete addition the reaction mixture was warmed to room temperature. The PMBO-lepidine salt is more stable than other PMB transfer reagents such as PMB chloride and PMB trichloroacetimidate. Also, the more hydrophobic lepidine salt was more soluble in $PhCF_3$ at room temperature. The *p*-methoxy group can stabilize the resultant carbocation formed from the decomposition of the salt. Therefore, the decomposition occurs readily at significantly lower temperatures. In case of alcohols, the reaction with PMBO-lepidine salt showed was formation of PMB ether at room temperature after addition of MeOTf. However, nitriles are relatively weaker nucleophiles compared to alcohols, therefore after addition of MeOTf at 0 °C, the reaction mixture was warmed to room temperature for 60 minutes, and finally it was transferred to an oil bath and the temperature was raised to 50 °C. The reaction mixture was then screened via TLC to analyze the consumption of nitrile.

Scheme 2.10: Reaction of nitrile and PMBO-lepidine Salt

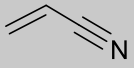
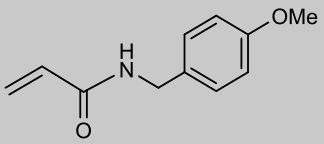
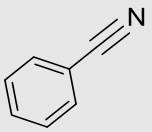
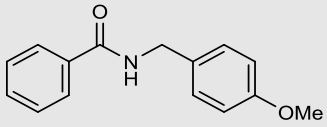
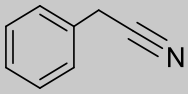
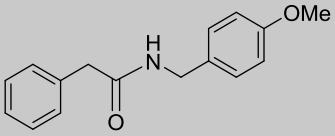


Since this was the first time that PMB-lepidine salt was studied in reaction with nitriles, the same nitriles showed the best results with BnOPT, acetonitrile and benzonitrile were selected for the initial analysis. The original procedure for these reactions was the same as the pathway showed in **Scheme 2.10**. This pathway was not successful for any of the selected nitriles and no sign of corresponding amide formation was seen. Additionally, TLC analysis did not prove the consumption of PMBO-lepidine even after 24h, which means no salt was formed or the salt was decomposed during the course of reaction. Therefore, the procedure was modified. In the new procedure PMB lepidine ether **(2.22)** in nitromethane was first treated by MeOTf dropwise at 0 °C to form the PMBO-lepidine salt following by addition of each of the nitrile in room temperature. There was a hypothesis that the salt might not be stable at higher temperatures, therefore the new conditions were completely the same as alcohols procedure which means the reaction mixture was screened in room temperature instead of 50 °C. As shown in Table 2.6, the conversion of nitriles **(2.1)** to corresponding amides **(2.24)** was even less than what was seen for in the case of BnOLT **(2.19)** for the same nitriles.

Table 2.6: Modified Procedure for Reaction of Nitriles with PMBO-lepidine Salt



(2.22) (2.1) (2.24)

2.22	Substrate	2.24	Product	2.24:2.22
a		**a**		-
b		**b**		1:10
c		**c**		1:15

The conflicting results when the alcohols switched to nitriles might be a result of the weaker nucleophilic characteristics of nitriles and could be concluded that higher reactivity of oxypyridinium salt might harm the reaction of nitriles as weaker nucleophiles. In other words, higher reactivity of PMBO-lepidine salt leads to faster decomposition and less efficient interaction between resultant PMB cation and the nitrile compound, which could highlight the importance of solubility as a factor in such reactions.

2.6 Conclusions

Before this project was started, oxypyridinium salts were known as efficient alkyl transfer reagents to a variety of nucleophiles.[16] Most notably, the reagent 2-benzyloxy-1-methylpyridinium triflate (BnOPT) was an excellent benzyl transfer reagent to both alcohols and carboxylic acids under relatively neutral conditions. These results led us to investigate the efficiency of these reagents in reaction with nitriles with the aim of amide synthesis under mild condition. But as we started our investigation there were always two important facts about nitriles that made them unique in reaction with oxypyridinium salts. First, nitriles are much weaker nucleophiles compared to alcohols or carboxylic acids, and second there is no way to activate the nucleophilicity of nitriles with adding external element to the reaction mixture. Based on previous hypothesis about mechanism of reaction, it was concluded that even with nitriles there should be no challenge for transferring alkyl group. In fact, it has been hypothesized that in S_N1-like mechanism with minor involvement of the nucleophile during the rate-determining step, even nitriles can be targeted for benzyl transfer. The results of different oxypyridinium salts in reaction with nitriles supported the viability of transferring benzyl and PMB groups through the S_N1-mechanism. Therefore, the weak nucleophilicity of nitriles does not exclude them as the nucleophilic candidate for S_N1-type reactions. However, to get better results with these weak nucleophiles, more efficient interaction with salt is needed. This implies that the solubility of oxypyridinium salt is the main issue with such reactions. On the other hand, several observations during the attempt for *N*-benzyl amide formation suggested that the mechanism for this reaction might have more S_N2-like characteristics unlike the proposed S_N1-like mechanism for the formation of benzyl ethers and benzyl esters. Higher yields and shorter reaction time needed for synthesis of benzyl ether compared to benzyl amide when the same oxypyridinium salt was consumed, proved that characteristics of nucleophile

could play a role in the reaction progress. Second, the difference in stability between PMB-lepidine salt and BnOPT may be an important factor when considering the involvement of the nucleophile in the rate-determining step. The higher reaction temperature in reaction with BnOPT would suggest that BnOPT is much more stable than PMB-lepidine salt. Therefore, it requires more energy for the decomposition of the BnOPT salt than it does for the PMB-lepidine salt which forms a carbocation that is highly stabilized through resonance and presence of methoxy group and anion stabilized by extended π-system. As a result, during the increased length of time required for the decomposition of BnOPT it is likely that the nucleophile can attack at an electrophilic site and assist in the loss of the pyridine species acting as a leaving group. This scenario is characteristic of a SN_2-like mechanism which is a concerted process. To sum up, although a series of experiments proved the possibility of *N*-benzylamide synthesis under mild condition using oxypyridinium salts, this conversion was challenging due to three main issues including the solubility issues of the salt, weak nucleophilicity of nitriles, and the instability of nitrilium ion. In fact, the conversion of nitriles to the corresponding amides presumed to proceed through nitrilium intermediate which introduces an issue of stability. Different experiments using BnOLT as a more hydrophobic salt were tested to overcome the solubility issues of BnOPT and to explore any limitations of benzyl transfer to the nitriles. PMB lepidine salt was also synthesized to monitor the effect of much more reactive salt on reaction progress. The results of this latter study suggested that the optimal balance between solubility and reactivity of oxypyridinium salt is needed in order to get the best interaction between the nitrile and the intermediate carbocation. In conclusion, although the conversion of nitriles to the amide under mild conditions is an important outcome, it is just the beginning of this story. To have a fully optimized reaction, all of the mentioned issues should be addressed in future. Performing the kinetics studies with both oxypyridinium salts and oxylepidinium salts could

potentially give a better idea of the mechanism of such conversion. Additionally, in future several more salt derivatives with higher solubility and less reactivity will be considered in the reaction with nitriles under mild conditions.

References

(1) Poon, K. W. C.; Dudley. G. B. Heat and Mix Benzylation of Alcohols Using a Bench-Stable Pyridinium Salt. *J. Org. Chem,* **2006**, *71*, 3923-3927

(2) Poon, K. W. C.; Albiniak, P. A.; Dudley, G. B. Protection of Alcohols Using 2-Benzyloxy-1-methylpyridiniuim trifluoromethanesulfonate: methyl (R)-(-)-3-benzyloxy-2-methyl-propanoate. *Org. Synth.* **2007,** *84*, 295-305.

(3) Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. Synthesis of Benzyl Esters Using 2-Benzyloxy-1-methylpyridinium Triflate. *J. Org. Chem.* **2007**, *72* (23), 8962-8964.

(4) Ritter, J. J.; Minieri, P. P. A New Reaction of Nitriles. I. Amides from Alkenes and Mononitriles1. *J. Am. Chem. Soc.* **1948**, *70* (12), 4045–4048.

(5) Poon, K. W. C.; House, S. E.; Dudley, G. B. A Bench-Stable Organic Salt for the Benzylation of Alcohols. *Synlett*. **2005,** *20*, 3142-3144.

(6) Dudley Benzylation Reagent. *Aldrich Chem Files*. **2007**, *7.3*, 3.

(7) Albiniak, P., Dudley, G. New Reagents for the Synthesis of Arylmethyl Ethers and Esters. *Synlett*. **2010**, 841-851.

(8) Walter, M.; Ramaley, L. Purification of Acetonitrile. *Anal. Chem.* **1973**, *45* (1), 165–166.

(9) Kidwai, M.; Mothsra, P. Neat Reaction Technology: A Green Tool. *Indian J. Chem.* **2006**, *45* (B), 2330–2336.

(10) Flint, L. *Synthesis and Inhibition Activity of N-Benzylbenzamide Derivatives against Tyrosinase*; California, **2009**.

(11) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons, **2007**.

(12) Marvel, C. S.; Lazier, W. A. Benzoyl Piperidine. *Org. Synth.* **1941**, *9*, 16.

(13) Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. Chemoselective Acylation of Amines in Aqueous Media. *European J. Org. Chem.* **2004**, *2004* (6), 1254–1260.

(14) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*, 5th ed.; John Wiley and Sons, **1995**.

(15) Nwoye, E. O.; Dudley, G. B. Synthesis of Para-Methoxybenzyl (PMB) Ethers under Neutral Conditions. *Chem. Commun.* **2007**, No. 14, 1436–1437.

(16) Lopez, S. S.; Dudley, G. B. Convenient Method for Preparing Benzyl Ethers and Esters Using 2-Benzyloxypyridine. *Beilstein J. Org. Chem.* **2008**, *4* (1), 44.

Appendix: Supporting Information regarding *N*-Benzyl Amide Synthesis

A_1: General Information Concerning Reagents and Instrumentation

All chemicals utilized to generate the data presented in this project were provided by Sigma-Aldrich, Acros, Fischer Scientific, or TCI. All glasswares, glass syringes, stir bars, and dispensing needles were dried in an oven at 110 °C for 24h and transferred to a desicator to cool off before use. Reactions were run under an argon atmosphere, on an IKA Hotplate or Optichem Digital Hotplate-Stirrer. Laboratory grease was added to the joints of flasks subjected to reflux conditions.

α,α,α-Trifluorotoluene was distilled from calcium hydride and stored under argon in an amber bottle over 4 Å molecular sieves. Toluene was dried in a VAC Atmospheres Solvent Purification System and stored in an argon purged amber bottle over molecular sieves. Nitromethane was fractionally distilled, followed by drying with $CaSO_4$. The pure solvent was then stored in an amber bottle in a cool place. Benzonitrile was purified by short path distillation.

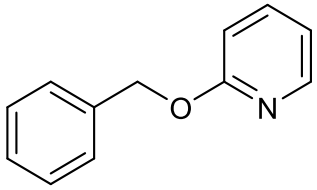
TLC plates from Sorbent Technologies (Aluminum back, Silica gel, UV 254, 20 μm) were used to monitor reactions for completion. A UV (254 nm) lamp, *p*-anisaldehyde stain (6 g anisaldehyde, 250 ml Ethanol, 2.5 ml conc. H_2SO_4), or $KMnO_4$ stain (1 g $KMnO_4$, 6.5 g K_2CO_3, 2 ml of 5% NaOH, 100 ml H_2O) or vanilin stain (6 g Vanillin, 2.5 conc. H_2SO_4, 250 ml Ethanol) were used to visualize compounds on TLC plates.

After completion of each reaction, work up was done to extract and collect products and possible byproducts. During extraction, all separated organic layers were dried using anhydrous sodium sulfate. A buchi Rotovapor was used to remove solvents. Any remaining solvent or water were evaporated using a low pressure vaccum pump.

Flash column chromatography with Dynamic Adsorbents Inc. flash silica gel was used for purification of products. Molecules were characterized by ^{1}H and ^{13}C NMR spectroscopy using a JEOL 300 MHz or 400 MHz instrument. Chloroform-D (D, 99.8% + 0.05% V/V TMS) from Cambridge Isotope Laboratories was used to solubilize all of the contents of each sample for all NMR spectra. Attenuated total reflection (ATR) was the sampling technique used in conjunction with IR spectroscopy on a Perkin Elmer Spectrum 100 FT-IR instrument.

All crude and pure materials were stored in Isotemp Fischer Scientific laboratory refrigerator at 2-8 °C when not in use.

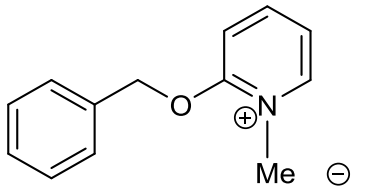
A_2: General Information Concerning Reactions and Characterizations and Experimental Data



(3.1)

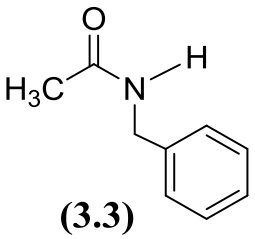
2-benzyloxypyridine (MB-I-4). A dry, 100-ml, round bottom flask was equipped with a stir bar, and an argon line. The flask was charged with a mixture of benzyl alcohol (3.13 g, 29.0 mmol), 2-chlorolepyridine (3.06 g, 27 mmol), KOH (4.9 g, 89 mmol, ground with a mortar and pestle), toluene (27 mL) and 18-crown-6 (71.3 mg, 0.27 mmol). The reaction was heated at reflux in an oil bath (115 °C) and allowed to stir until the benzyl alcohol was completely consumed as indicated by TLC analysis. The reaction mixture was diluted in ethyl acetate or diethyl ether (20 ml) and filtered through a celite "packed" fritted funnel which was subsequently rinsed with the organic solvent. The filtrate was transferred to a separatory funnel where it was washed with water (2 x 20 ml) followed by brine (20 ml). The organic layer was dried over anhydrous sodium sulfate which was removed by vacuum filtration. The filtrate was collected in a pre-weighed round bottom flask and concentrated on the rotary evporator to yield the crude material.^{1}H NMR of the crude product was obtained. Flash column chromatography with a 19:1 ratio of hexanes to ethyl acetate was used to purify the crude material to yield the pure 2-benzyloxypyridine as a colorless oil (4.60 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (ddd, *J* = 5.0, 1.3, 1.1 Hz, 1 H), 7.58 (ddd, *J* = 7.6, 1.8, 1 Hz, 1 H), 7.46 (d, *J* = 7.1 Hz, 2 H), 7.30-7.40 (m, 3 H), 6.88 (ddd, *J* = 7.6, 5.07, 1.7 Hz, 1 H), 6.82 (dd, *J* = 8.3, 1.6 Hz, 1 H), 5.38 (s, 2 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 146.9, 138.7, 137.4,

128.5, 128.0, 127.9, 117.0, 111.4, 67.6. IR (neat cm^{-1}) 3032, 2941, 2880, 1737, 1594, 1569, 1473, 1430, 1284, 1142, 987, 777, 695.



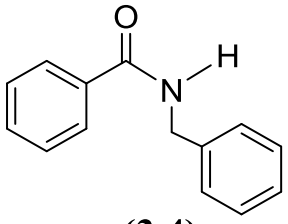
(3.2)

2-benzyloxy-1-methylpyridinium triflate (MB-I-5). A dry, single neck, 100-ml round bottom flask equipped with a stir bar was purged with argon before adding 2-benzyloxypyridine (2.65 g, 14.3 mmol), and trifluorotoluene (29 ml). The reaction flask was then brought to 0 °C in an ice bath before the dropwise addition of MeOTf (1.78 ml, 15.7 mmol) over 15 minutes. The reaction was removed from the ice bath after complete addition of MeOTf and allowed to stir at room temperature. The reaction progression was monitored by TLC which indicated it had reached completion after 1.5h. The reaction mixture was then washed using hexane (10 ml). Vacuum filtration was used to collect and dry the white solid product (4.75 g, 95%) on a Whatman filter paper. The product was then transferred to a pre-weighed round bottom flask and placed under high vaccum to remove all of the remaining moistures. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 6.6, 1.8 Hz, 1 H), 8.32 (ddd, *J*= 8.7, 6.7, 1.9 Hz, 1 H), 7.63 (d, *J* = 8.7, 1 H), 7.44 (m, 6 H), 5.56 (s, 2 H), 4.1 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.1, 144.0, 132.5, 129.9, 129.3, 128.8, 119.3, 112.3, 74.8, 42.3. IR (neat cm^{-1}) 3084, 3050, 1637, 1586, 1519, 1440, 1261, 1147, 1030, 1013, 768, 696.



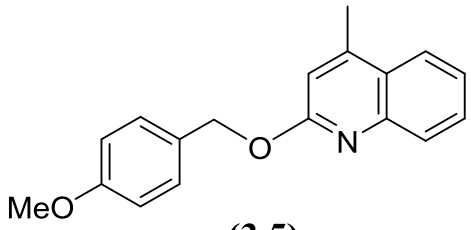
(3.3)

***N*-benzylacetamide (MB-I-23).** A dry, single neck, 10-ml round bottom flask equipped with a stir bar was purged with argon before adding acetonitrile (82 mg, 2 mmol), and BnOPT salt (470 mg, 1.34 mmol). The reaction flask was equipped with a condenser and heated at reflux in a silicone oil bath (83 °C). The reaction was monitored by TLC which indicated it had reached completion after 24h. The reaction mixture was transferred to a separatory funnel using diethyl ether (10 ml) then washed with water (10 ml) and brine (10 ml). The organic layer was dispensed into an Erlenmeyer flask and dried over anhydrous sodium sulfate. Vacuum filtration was used to remove the drying agent and the filtrate was collected in a pre-weighed round bottom flask which was concentrated on a rotary evaporator to yield a light yellow liquid. Flash column chromatography with a 9:1 ratio of hexanes to ethyl acetate was used for give a pure light yellow liquid (0.088 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.36 (m, 5 H), 5.70 (br s, 1 H), 4.43 (d, *J* = 5.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.1, 128.7, 127.9, 127.8, 43.9, 23.6. IR (neat cm^{-1}) 3290, 3064, 3032, 1645, 1539, 1497, 1357, 1281, 1096, 731, 694.



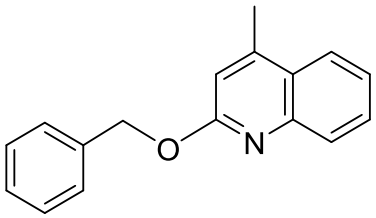
(3.4)

***N*-benzylbenzamide (MB-I-25).** A dry, single neck, 10-ml round bottom flask equipped with a stir bar was purged with argon before adding benzonitrile (146 mg, 1.42 mmol), and BnOPT salt (330 mg, 0.94 mmol). The reaction flask was heated in a silicone oil bath (83 °C). The reaction was monitored by TLC which indicated it had reached completion after 24h. The reaction mixture was transferred to a separatory funnel using diethyl ether (10 ml) then washed with water (10 ml) and brine (10 ml). The organic layer was dispensed into an Erlenmeyer flask and dried over anhydrous sodium sulfate. Vacuum filtration was used to remove the drying agent and the filtrate was collected in a pre-weighed round bottom flask which was concentrated on a rotary evaporator to yield a white liquid. Flash column chromatography with a 9:1 ratio of hexanes to ethyl acetate was used for give a pure light yellow liquid (71 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2 H), 7.51-7.35 (m, 8 H), 6.37 (br s, 1 H), 4.65 (d, J = 5.8, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 138.2, 134.3, 131.8, 129.1, 129, 127.8, 127.7,126.1, 44.2. IR (neat cm^{-1}) 3319, 3058, 1725, 1639, 1577, 1538, 1488, 1451, 1296, 1001, 989, 726, 690.



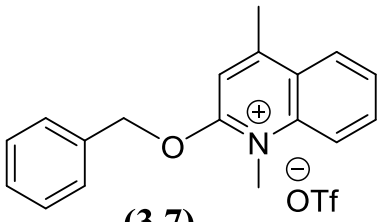
(3.5)

2-(4-Methoxybenzyloxy)-4-methylquinoline (MB-I-112). A mixture of 4-methoxybenzyl alcohol (3.6 g, 26 mmol), 2-chlorolepidine (3.6 g, 21 mmol), KOH (4.8 g, 86 mmol, ground with a mortar and pestle), toluene (41 mL) and 18-crown-6 (318 mg, 1.2 mmol) was heated at reflux in an oil bath (115°C) for 1.5 h. The reaction mixture was then cooled to room temperature and diluted in ethyl acetate (50 mL) and filtered through a celite "packed" fritted funnel which was subsequently rinsed with the organic solvent. The filtrate was transferred to a separatory funnel where it was washed with water (2 x 20 ml) followed by brine (20 ml). The organic layer was dried over sodium sulfate which was removed by vacuum filtration. The filtrate was collected in a pre-weighed round bottom flask and concentrated on the rotary evporator to remove remaining solvents.^{1}H NMR of the crude product was obtained. Flash column chromatography with a 4:1 ratio of hexanes to ethyl acetate was used to purify the crude material to provide **(3.5)** as a white solid (5.1 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2 H), 7.62 (td, *J* = 7.2,1.3 Hz, 1 H), 7.49–7.40 (m, 3 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 6.79 (s, 1 H), 5.46 (s, 2H), 3.81 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 159.7, 147.0, 146.8, 130.1, 129.3, 129.2, 127.8, 125.9, 123.8, 123.7, 113.9,113.3, 67.2, 55.4, 18.8. IR (neat cm^{-1}) 3008, 2954, 1610, 1584, 1572, 1513, 1439, 1393, 1326, 1257, 1174, 1031, 842, 755.



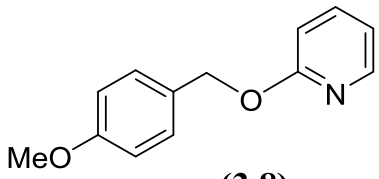
(3.6)

2-benzyloxylepidine (MB-I-83). A dry, single neck, 50-ml round bottom flask equipped with a stir bar was purged with argon before adding 2-chlorolepidine (3.50 g, 20 mmol), benzyl alcohol (2.37 g, 22 mmol), and triflourotoluene (20 ml). Potassium hydroxide (3.7 g, 66 mmol) pellets were crushed using a mortar and pestle then added to the reaction flask followed by 18-crown-6 (0.052 g, 0.2 mmol). The reaction flask was equipped with a condenser and heated at reflux (115 °C) in a silicone oil bath. The reaction was monitored by TLC which indicated it had reached completion after 3h. The reaction mixture was transferred to a separatory funnel using ethyl acetate (20 ml) then washed with water (2 x 20) and brine (20 ml). The organic layer was dispensed into an Erlenmeyer flask and dried over anhydrous sodium sulfate. Vacuum filtration was used to remove the drying agent and the filtrate was collected in a pre-weighed round bottom flask which was concentrated on a rotary evaporator to yield a light yellow liquid. Flash column chromatography with a 19:1 ratio of hexanes to ethyl acetate afforded **(3.6)** as a light green oil (4.25 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9, 2 H), 7.62 (td, *J*= 15.3, 1.5 Hz, 1 H), 7.51 (d, *J* = 7.7, 2 Hz, 1H), 7.45-7.30 (m, 4 H), 6.82 (s, 1 H), 5.56 (s, 2 H), 2.58 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 147, 146.9, 137.9, 129.7, 128.8, 128.6, 128.5, 125.8, 125.1, 124.0, 113.8, 67.7, 18.9. IR (neat cm^{-1}) 3062, 3032, 2954, 1611, 1574, 1470, 1394, 1333, 1253, 1175, 906, 855, 751, 665.



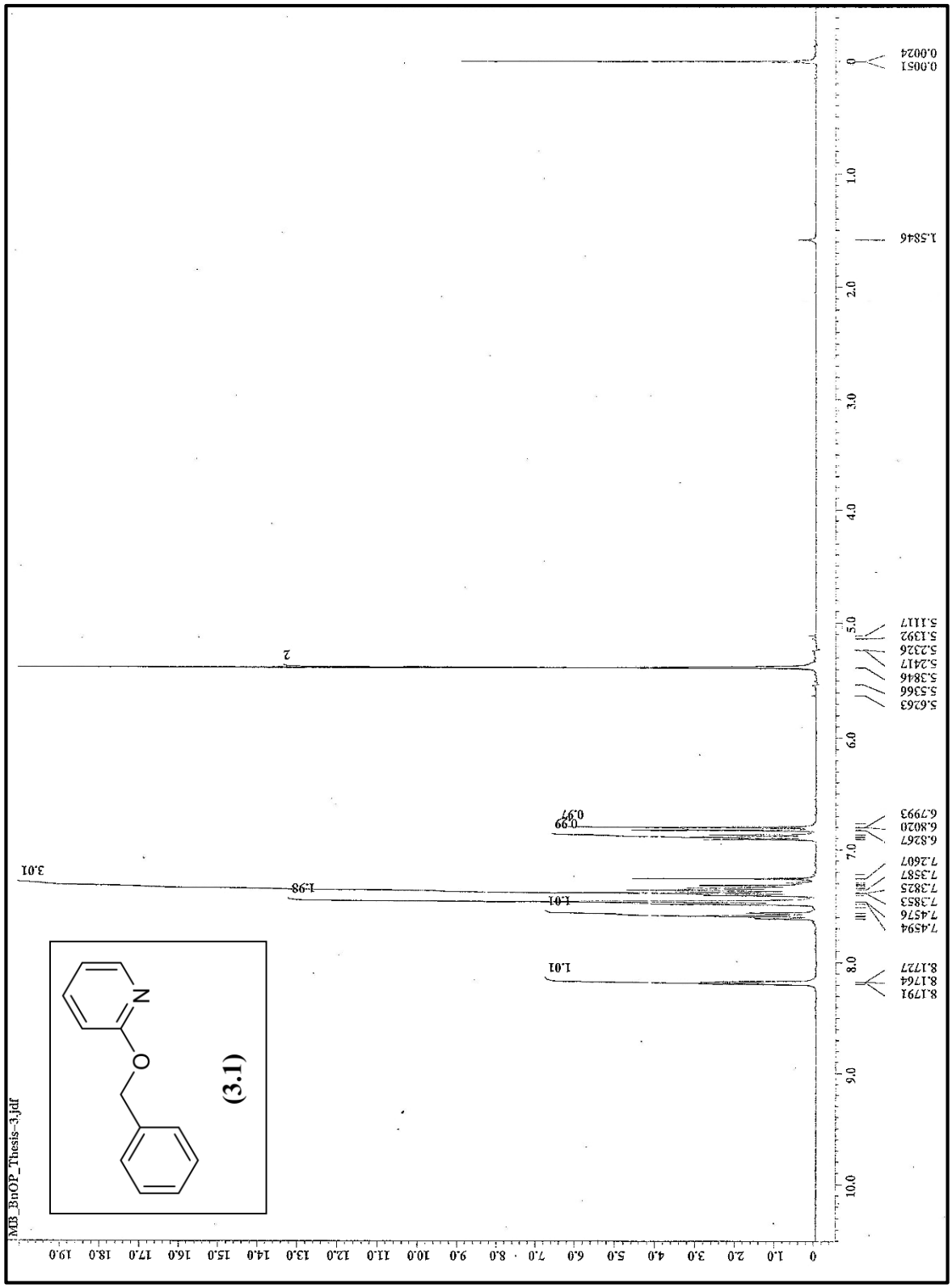
(3.7)

2-benzyloxy-1-methyllepidinium triflate (MB-I-86). A dry, single neck, 100-ml round bottom flask equipped with a stir bar was purged with argon before adding 2-benzyloxylepidine (2.42 g, 9.7 mmol), and triflourotoluene (19 ml). The reaction flask was then brought to 0 °C in an ice bath before the dropwise addition of MeOTf (2.19 ml, 20 mmol) over 30 minutes. The reaction was removed from the ice bath after complete addition of MeOTf and allowed to stir at room temperature. The reaction progression was monitored by TLC which indicated it had reached completion after 2.5h. The reaction mixture was then washed using hexane (50 ml). Vacuum filtration was used to collect and dry the white solid product (3.8 g, 95%) on a Whatman filter paper. The product was then transferred to a pre-weighed round bottom flask and placed under high vaccum to remove all of the remaining volatiles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1 H), 7.95-8.05 (m, 2 H), 7.84 (s, 1 H), 7.77 (ddd, *J* = 7.7, 6.04, 2.40 Hz, 1 H), 7.56 (dd, *J* = 6.3, 2.14 Hz, 2 H), 7.45 (t, *J* = 3.5 Hz, 3 H), 5.84 (s, 2 H), 4.2 (s, 3H), 2.96 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 160.1, 137.8, 135.4, 132.6, 129.9, 129.0, 128.8, 127.8, 127.0, 124.4, 118.7, 110.6, 75.7, 34.0, 20.2. IR (neat cm^{-1}) 3087, 1610, 1589, 1523, 1422, 1373, 1259, 1160, 1027, 898, 764, 692.



(3.8)

4-Methoxybenzyloxy pyridine (MB-I-118). A mixture of 4-methoxybenzyl alcohol (3.8 g, 27.5 mmol), 2-chloropyridine (2.8 g, 25 mmol), KOH (4.6 g, 82.5 mmol, ground with a mortar and pestle), toluene (25 mL) and 18-crown-6 (66 mg, 0.25 mmol) was heated at reflux (115°C) for 2 h. The reaction mixture was then cooled to room temperature and diluted in ethyl acetate (25 mL) and filtered through a celite "packed" fritted funnel which was subsequently rinsed with the organic solvent. The filtrate was transferred to a separatory funnel where it was washed with water (2 x 20 ml) followed by brine (20 ml). The organic layer was dried over sodium sulfate which was removed by vacuum filtration. The filtrate was collected in a pre-weighed round bottom flask and concentrated on the rotary evporator to remove remaining solvents.^{1}H NMR of the crude product was obtained. Flash column chromatography with a 4:1 ratio of hexanes to ethyl acetate was used to purify the crude material to provide **(3.8)** as a white solid (4.7 g, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1 H), 7.57 (ddd, *J* = 8.6, 7.6, 2.0 Hz, 1 H), 7.39 (d, *J* = 8.6 2 H), 6.88 (m, 3 H), 6.78 (dt, *J* = 8.4, 1.0, 1 H), 5.28 (s, 2H), 3.82 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164, 159.9, 146.9, 138.6, 128.8, 128,5, 116.9, 113.9, 111.4, 67.4, 55.3. IR (neat cm^{-1}) 3007, 2936, 2835, 1607, 1592, 1513, 1431, 1364, 1241, 1173, 985, 877, 777, 736.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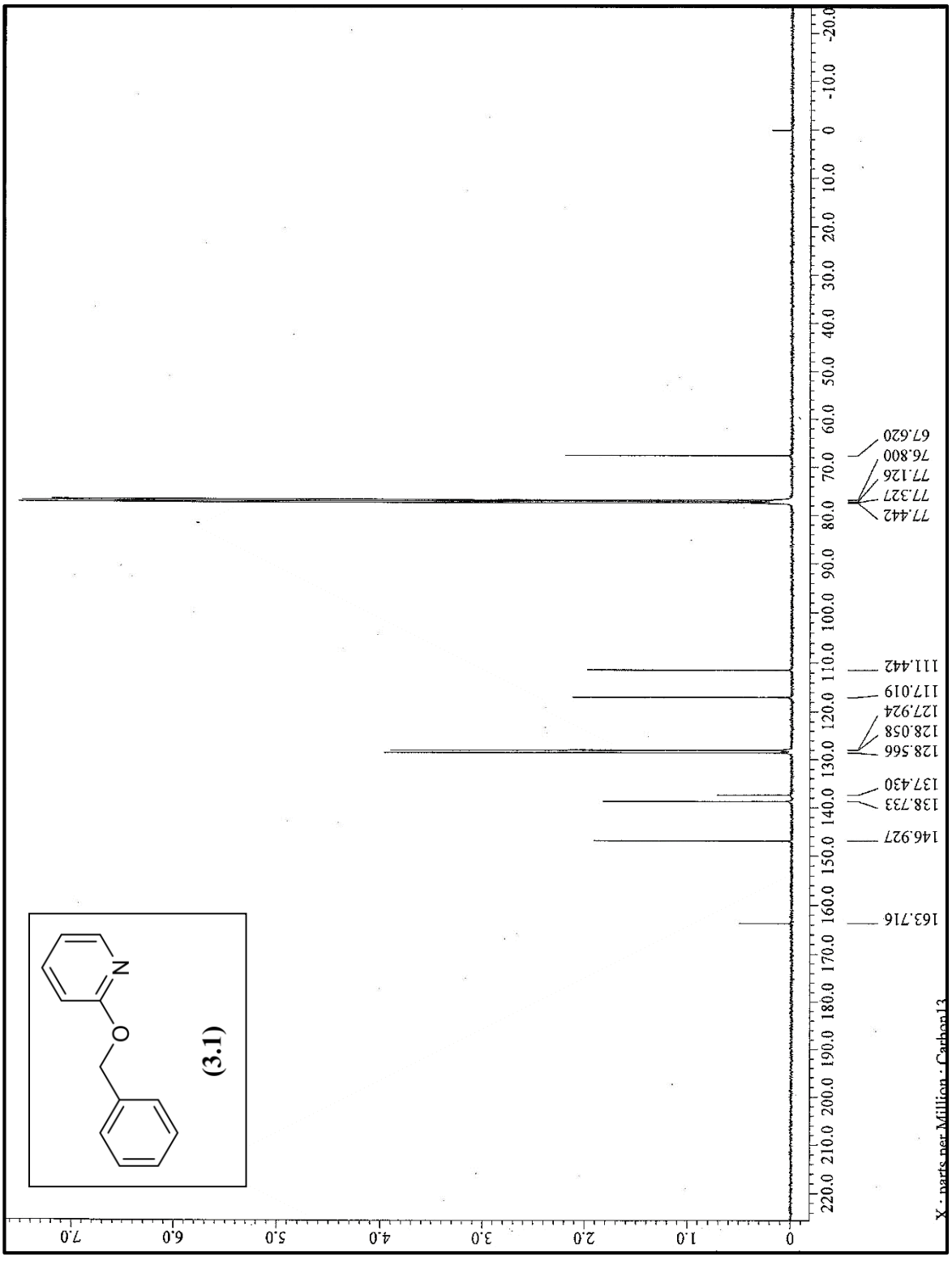
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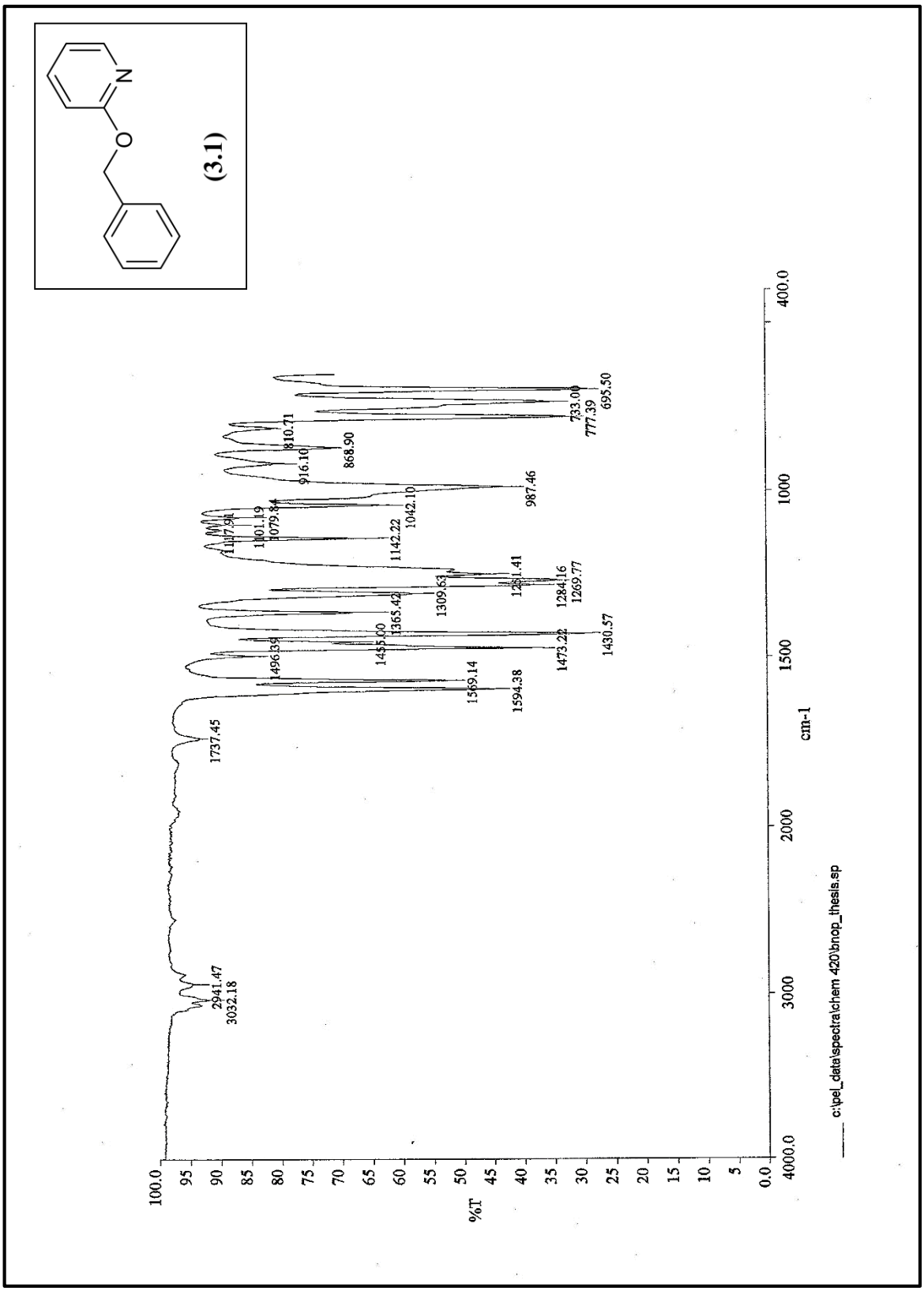
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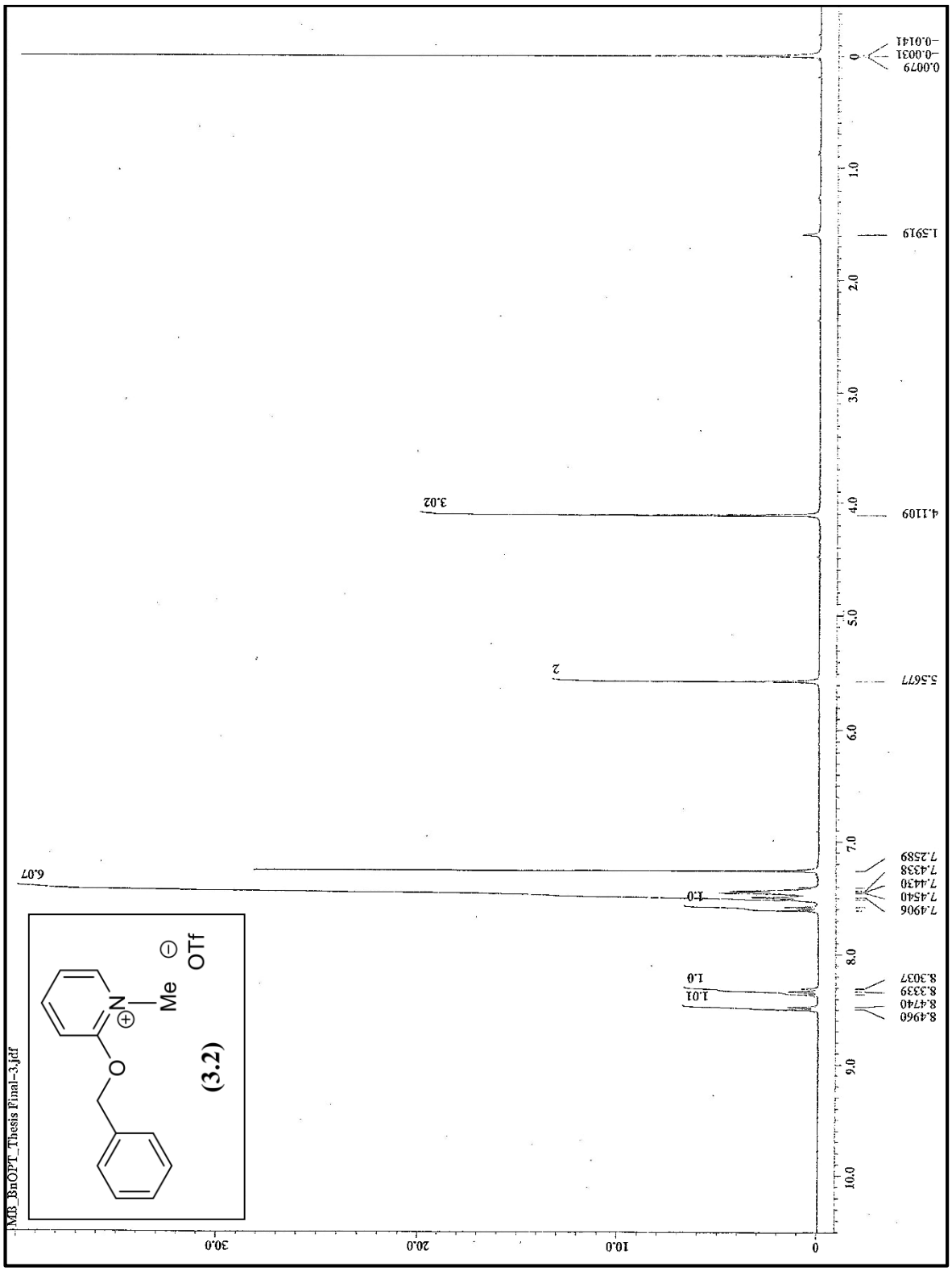
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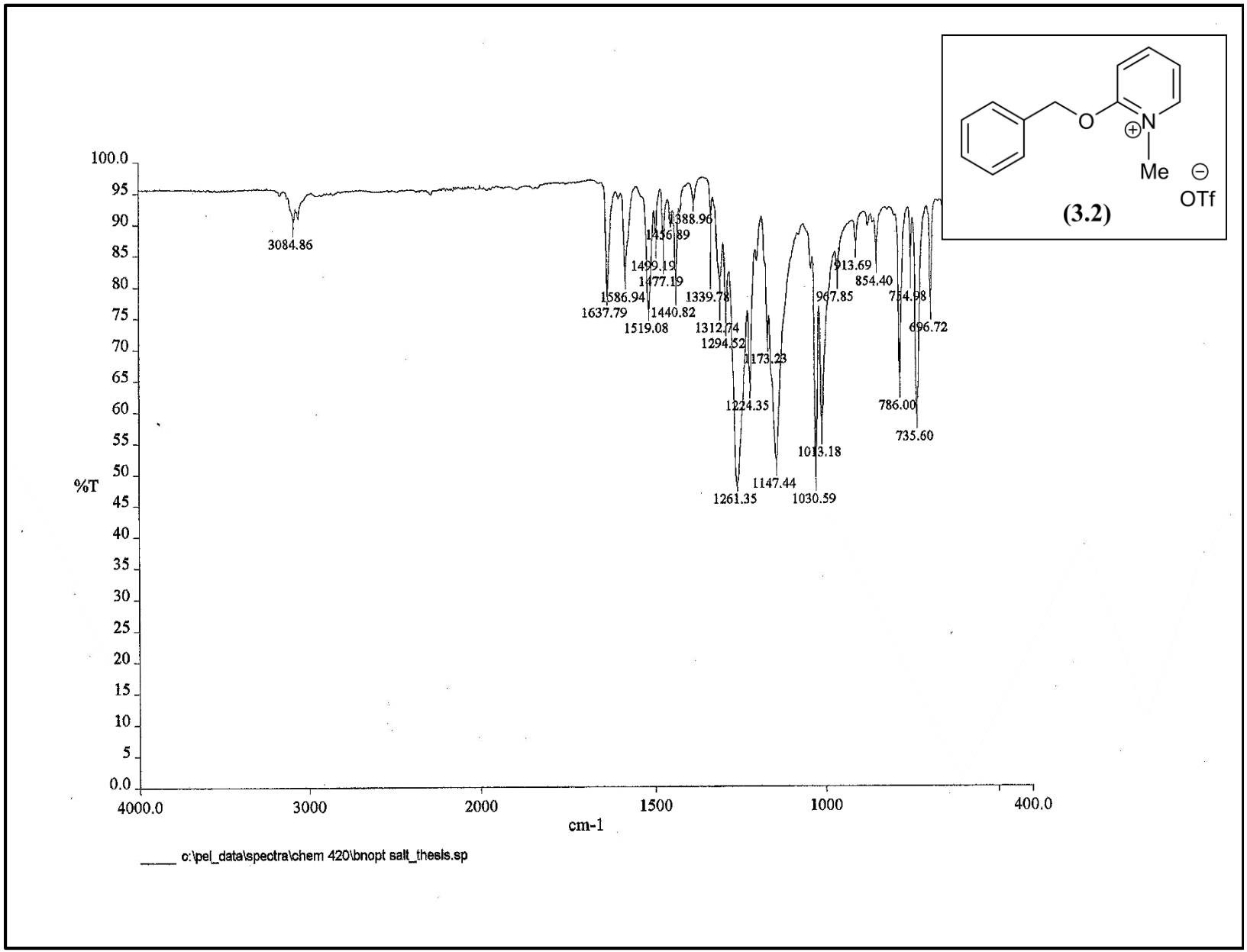
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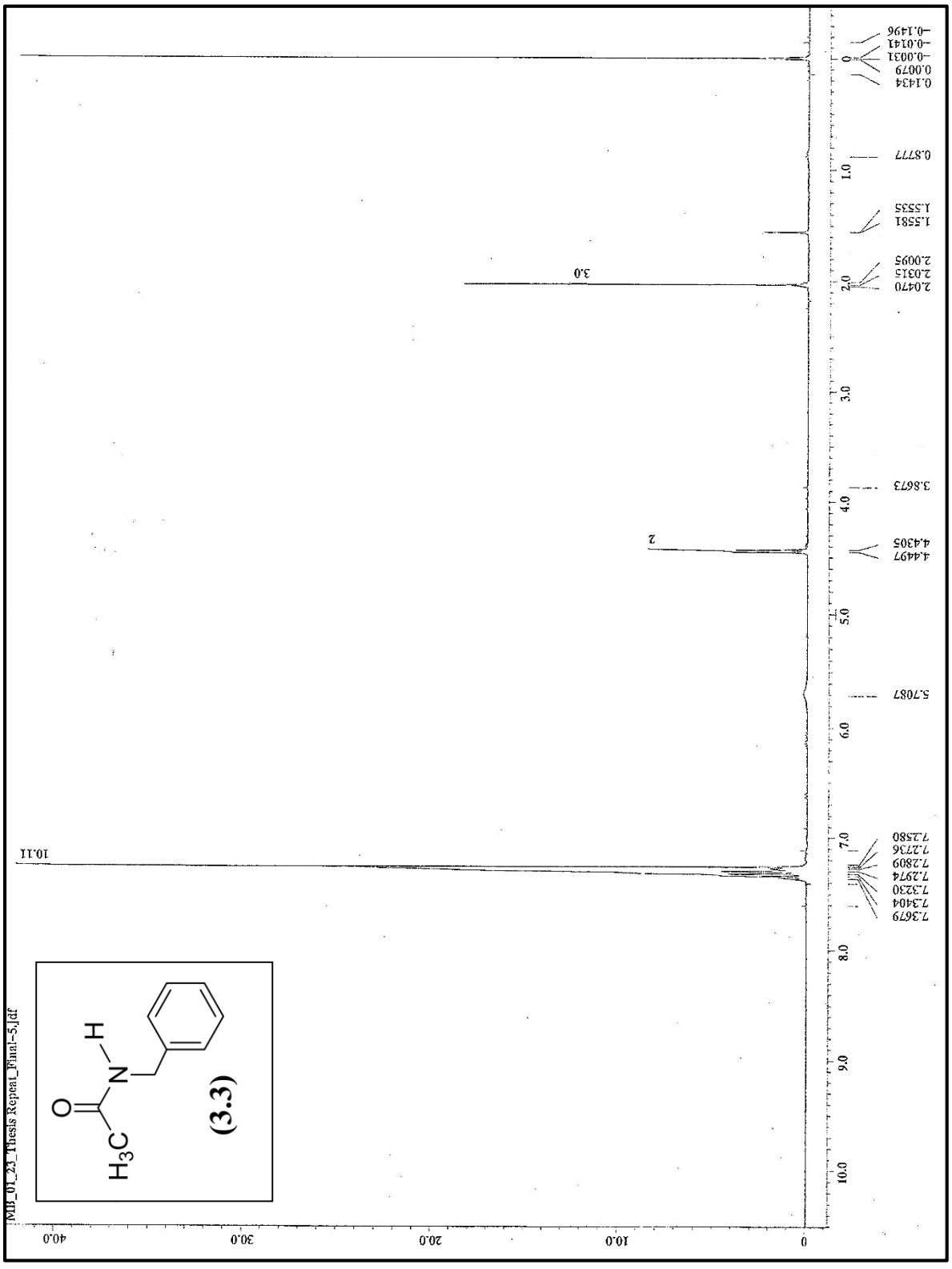
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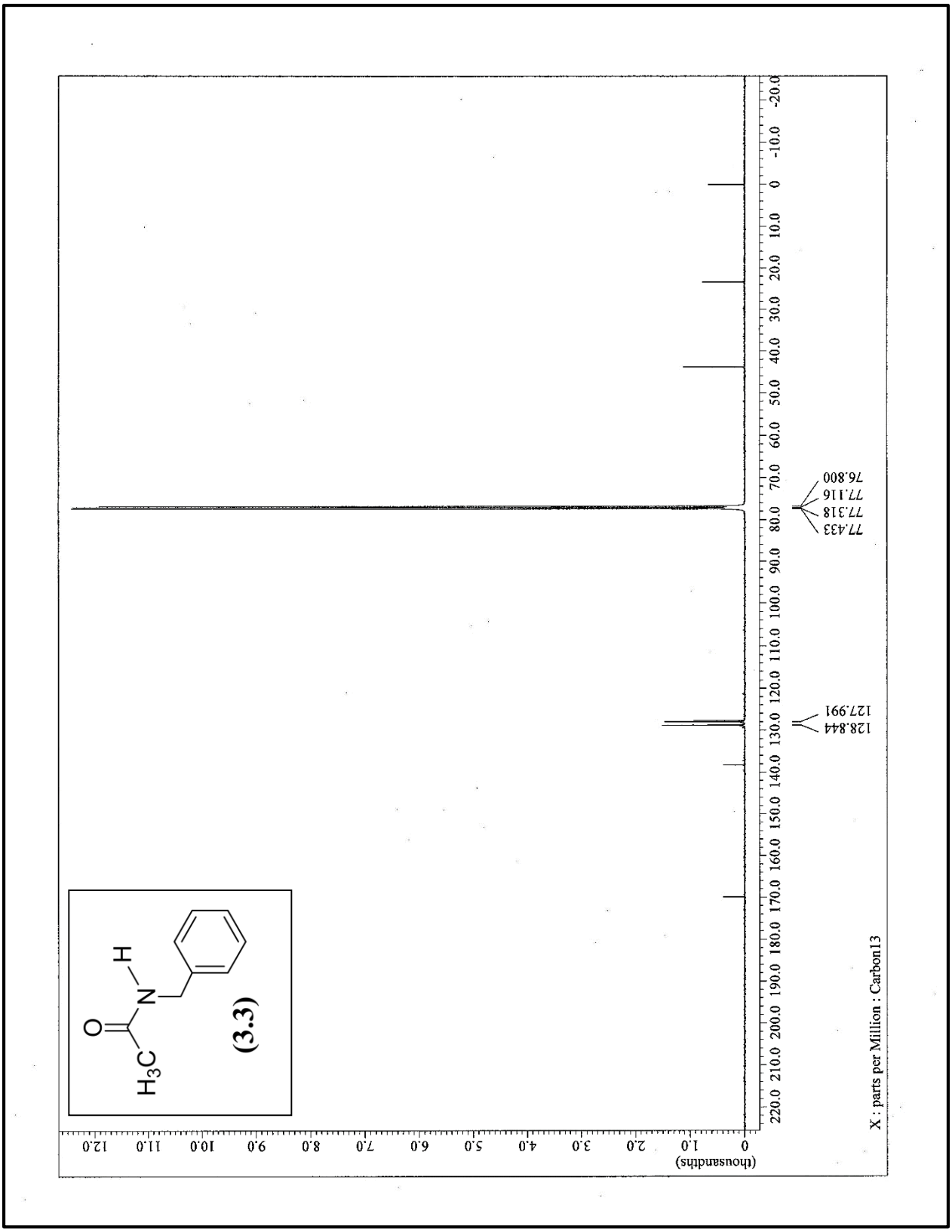
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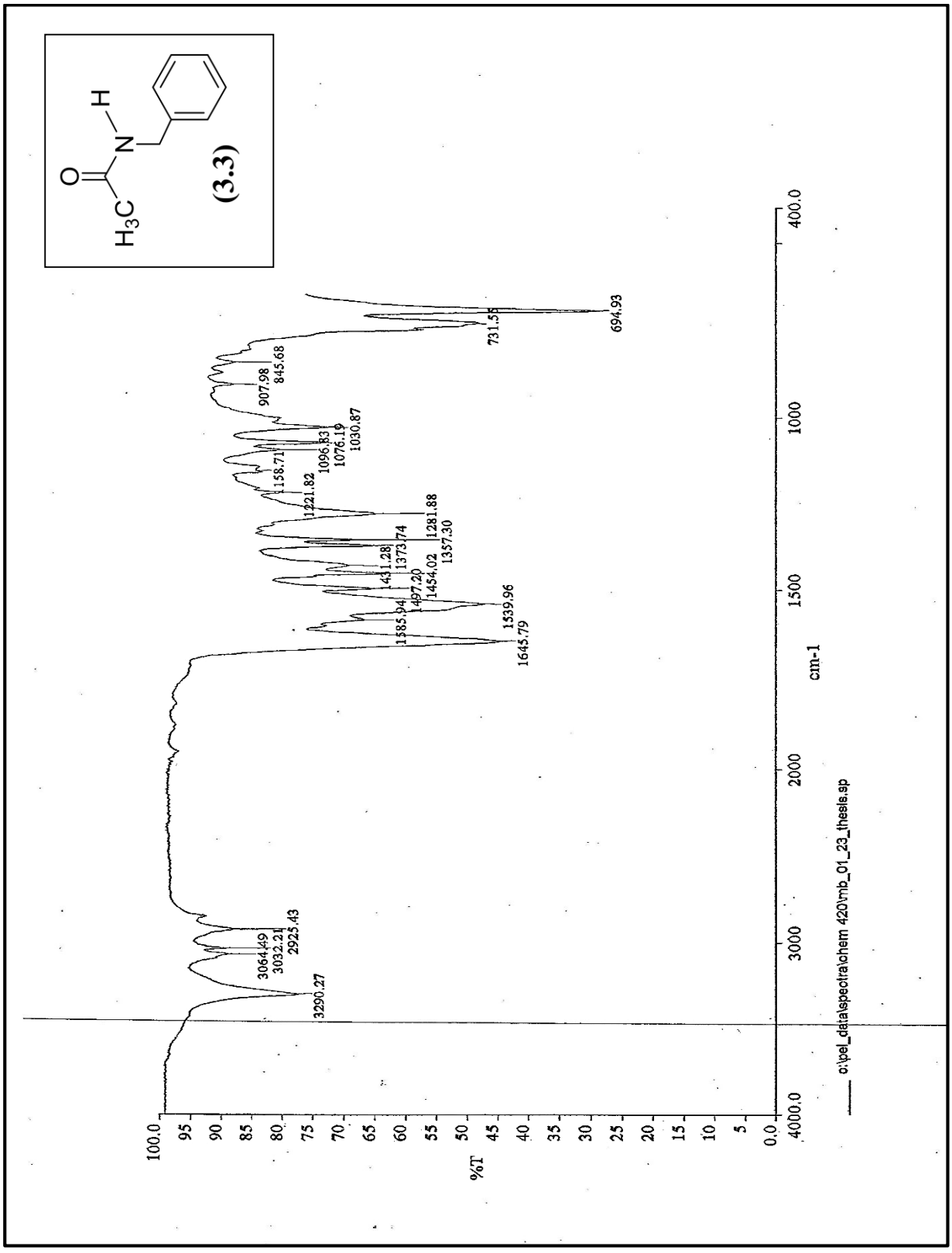
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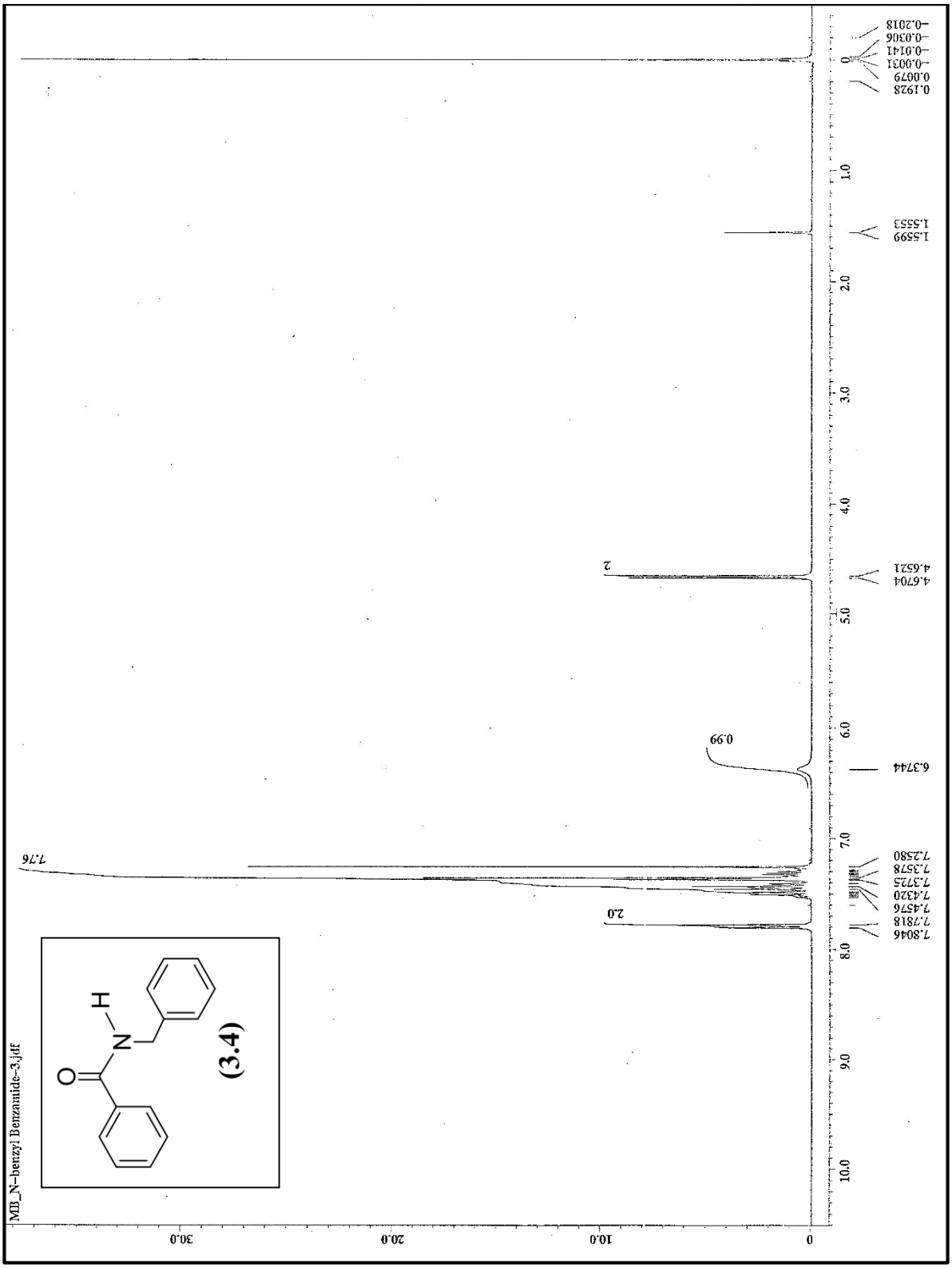
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(Thousands)
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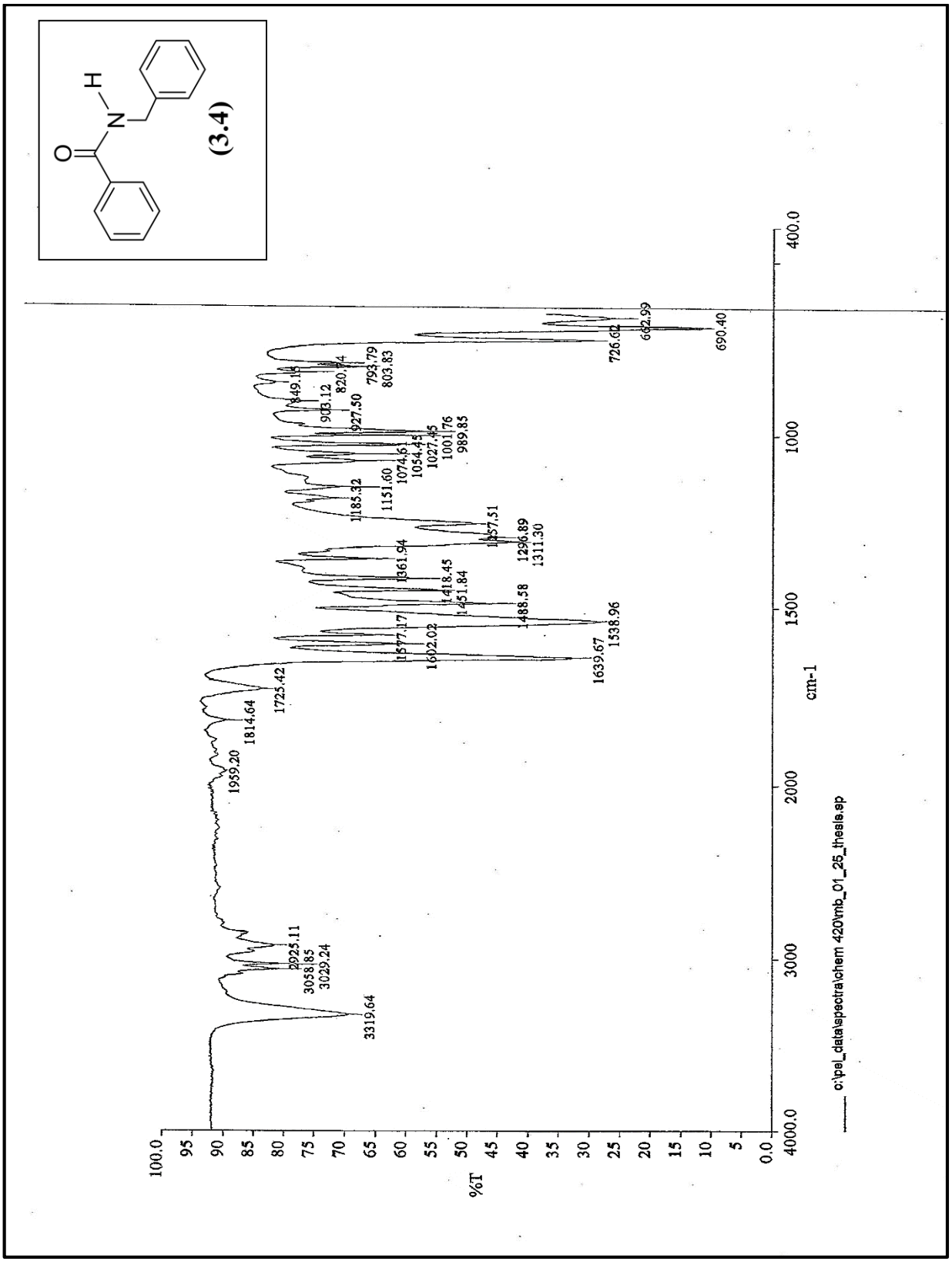
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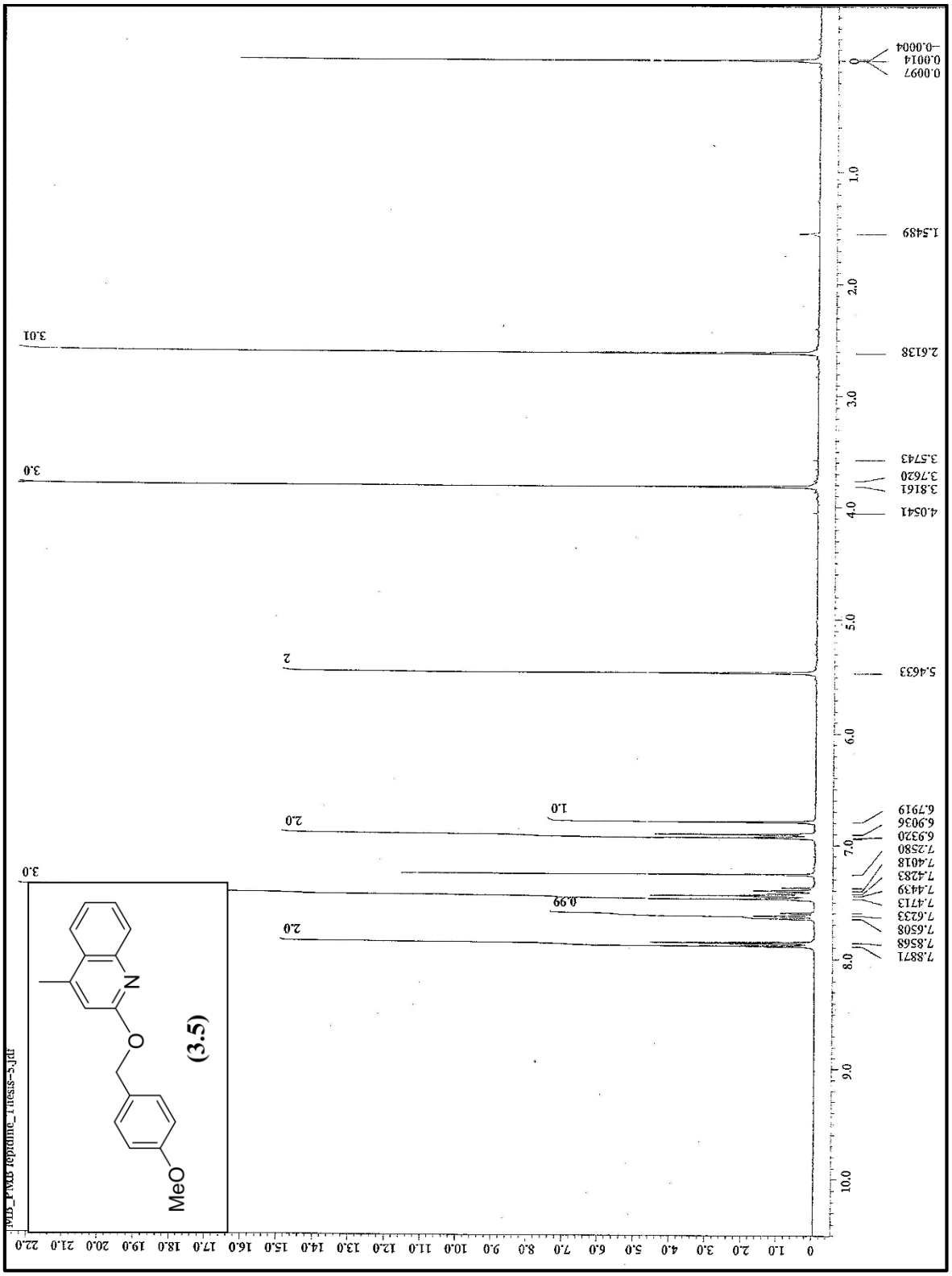
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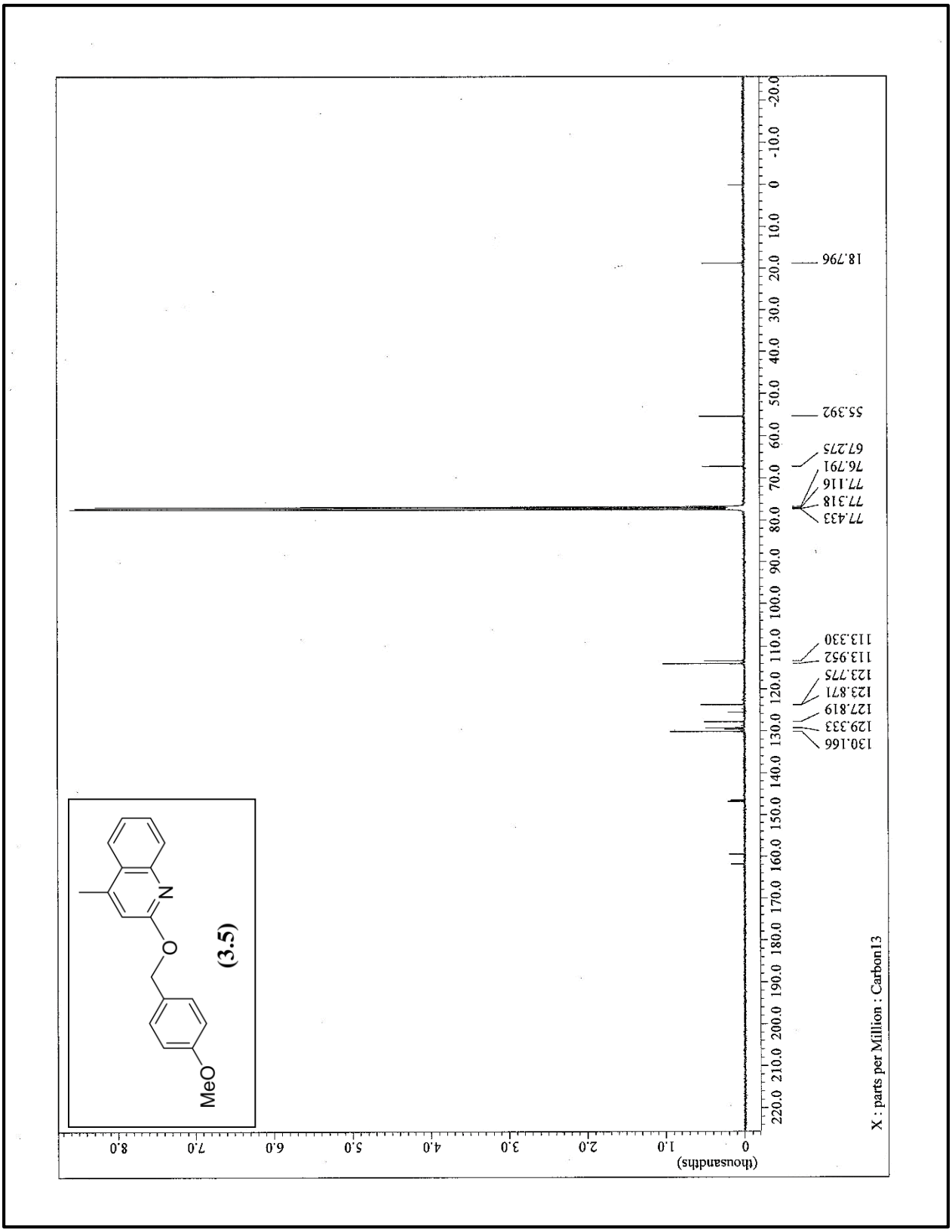
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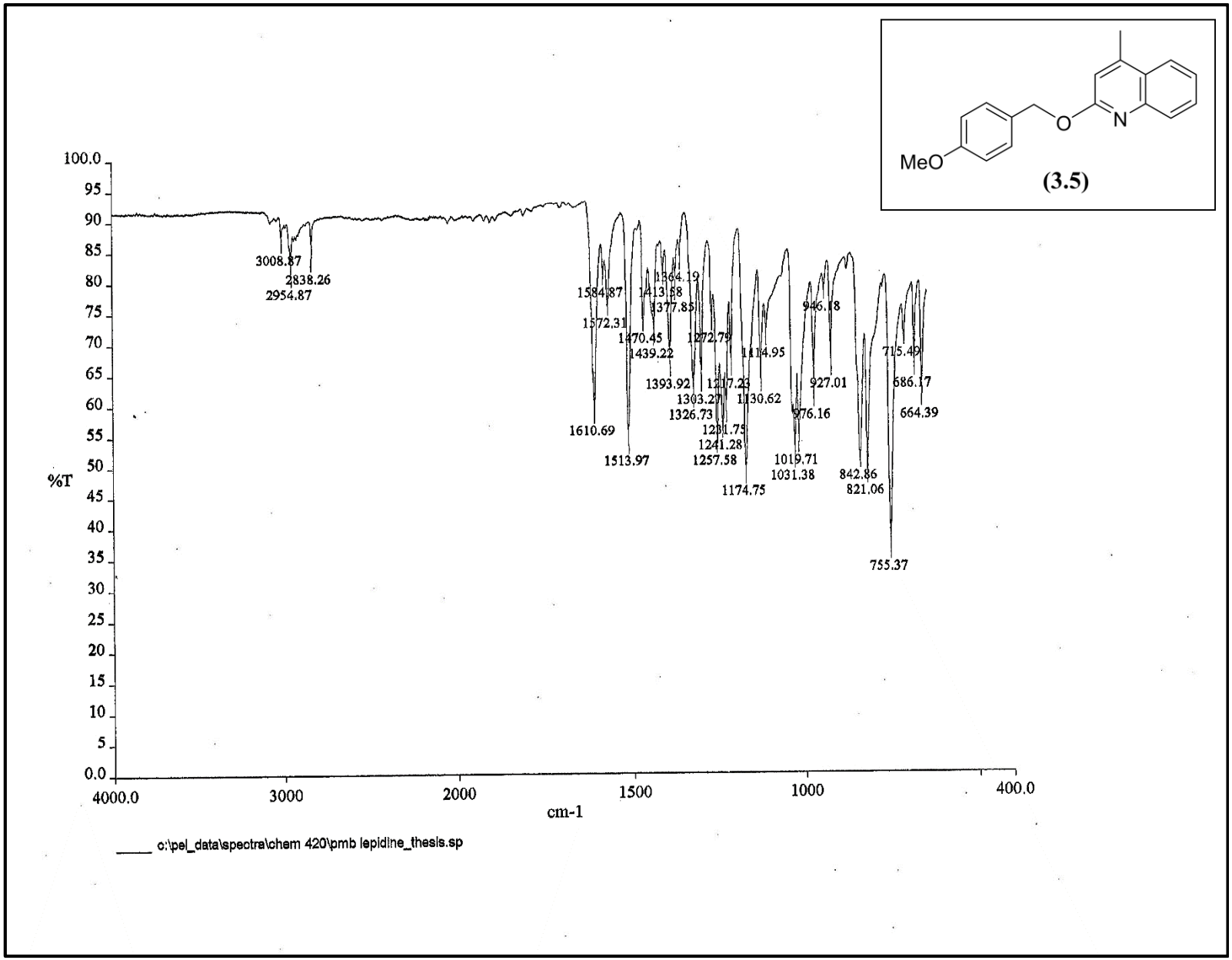
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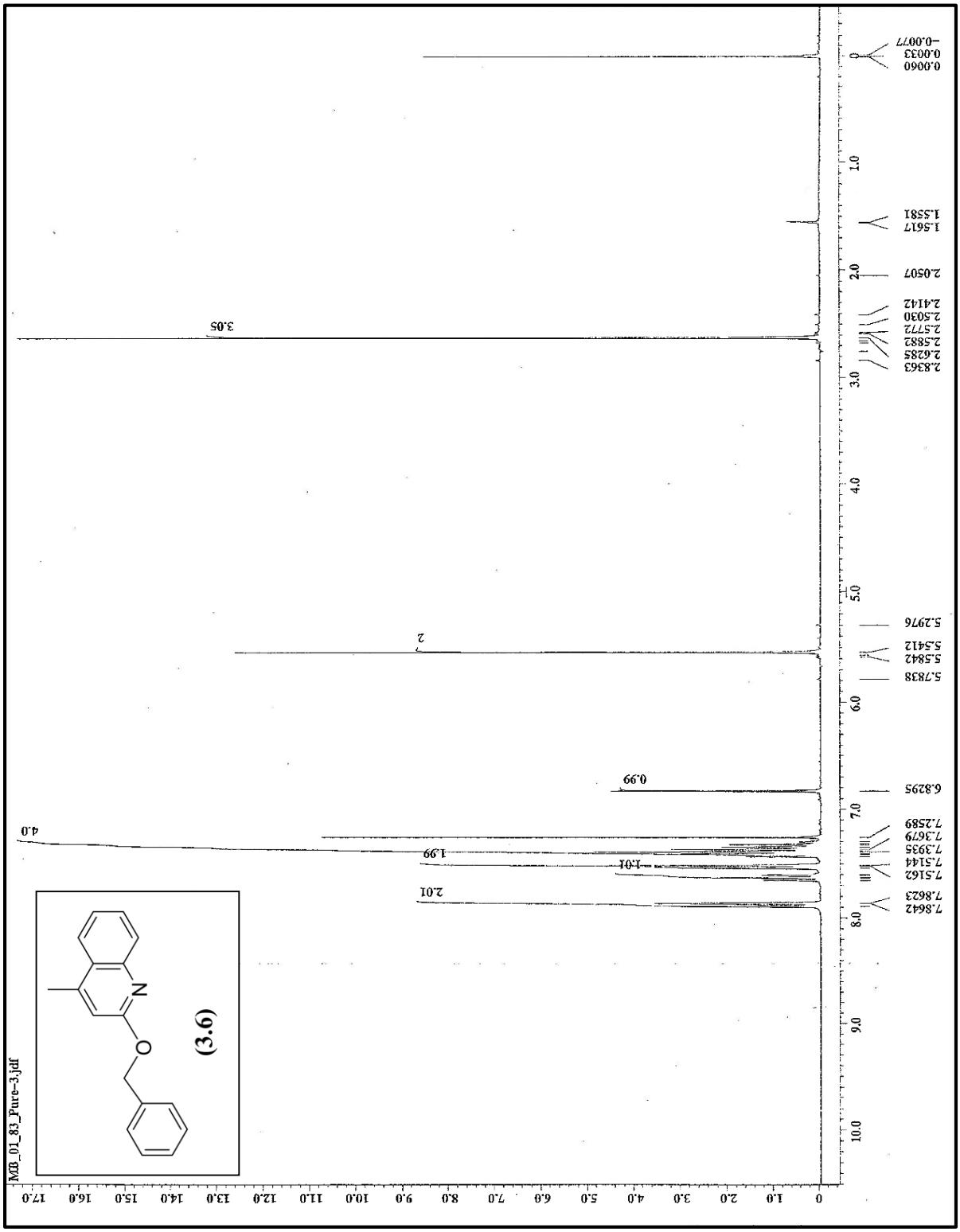
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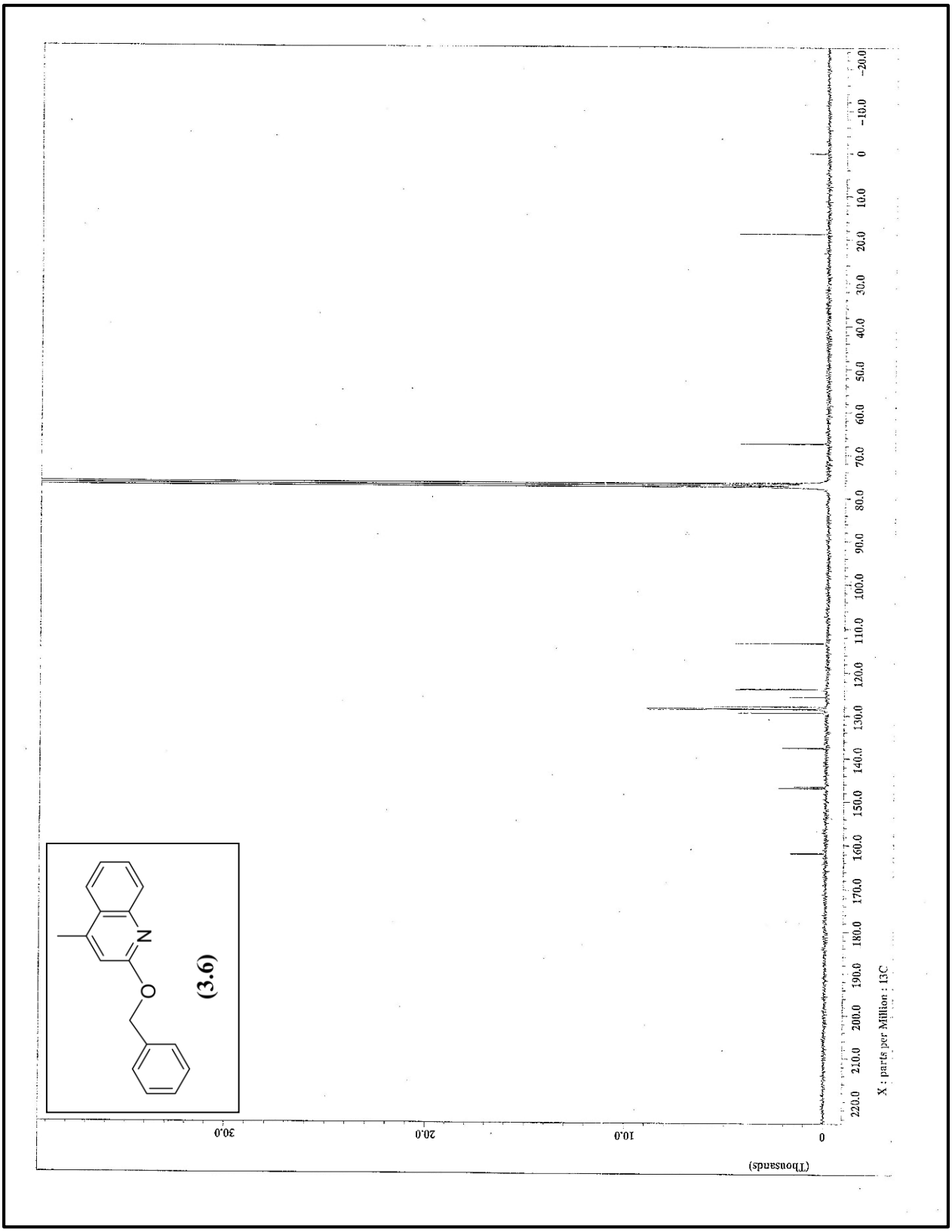
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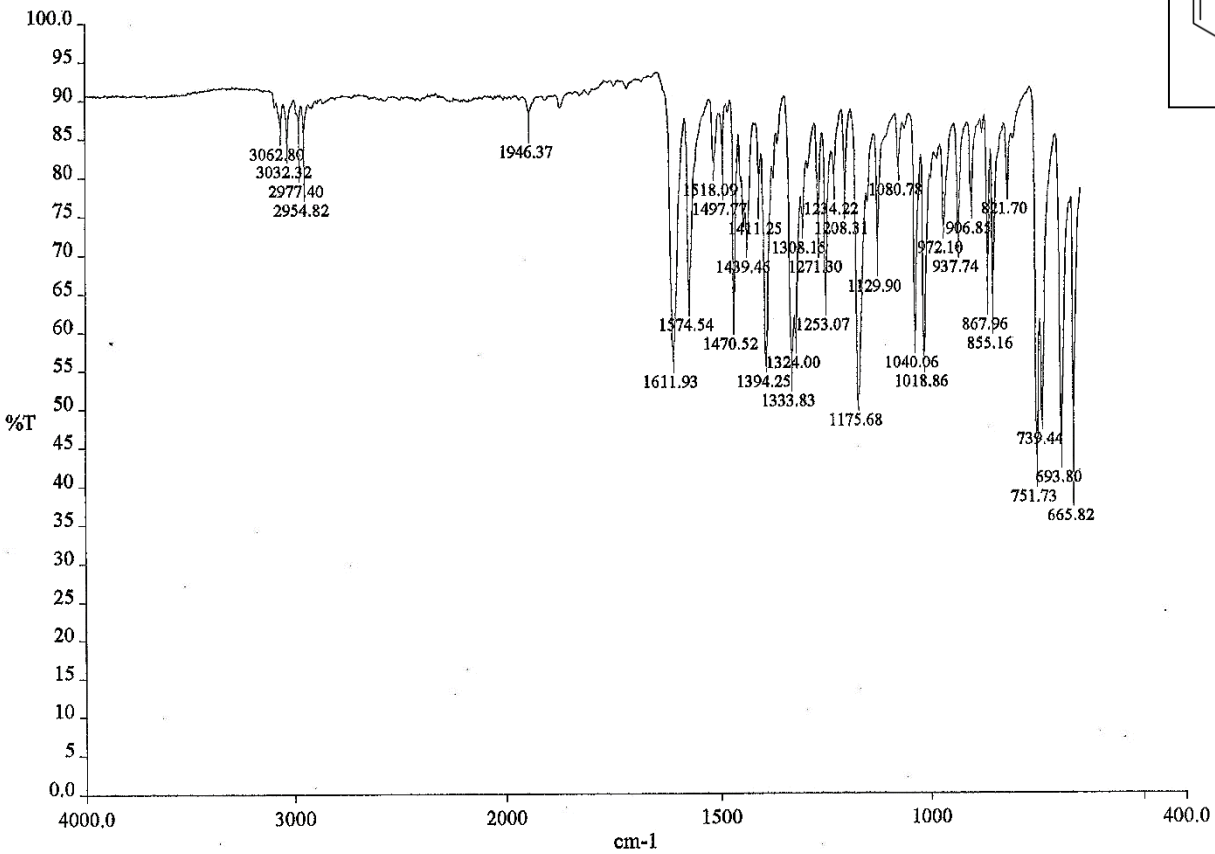
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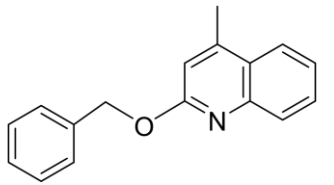
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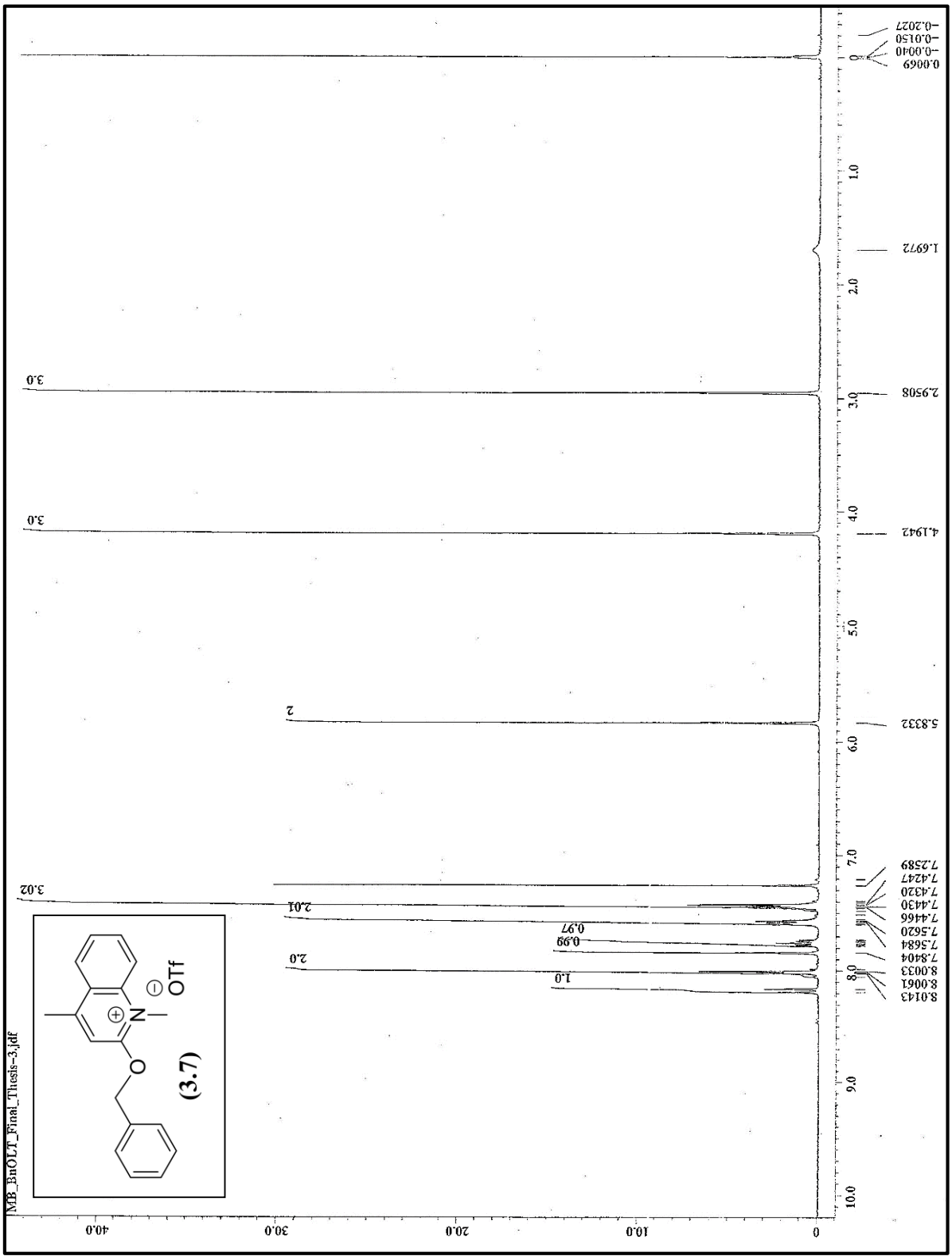
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(Thousands)
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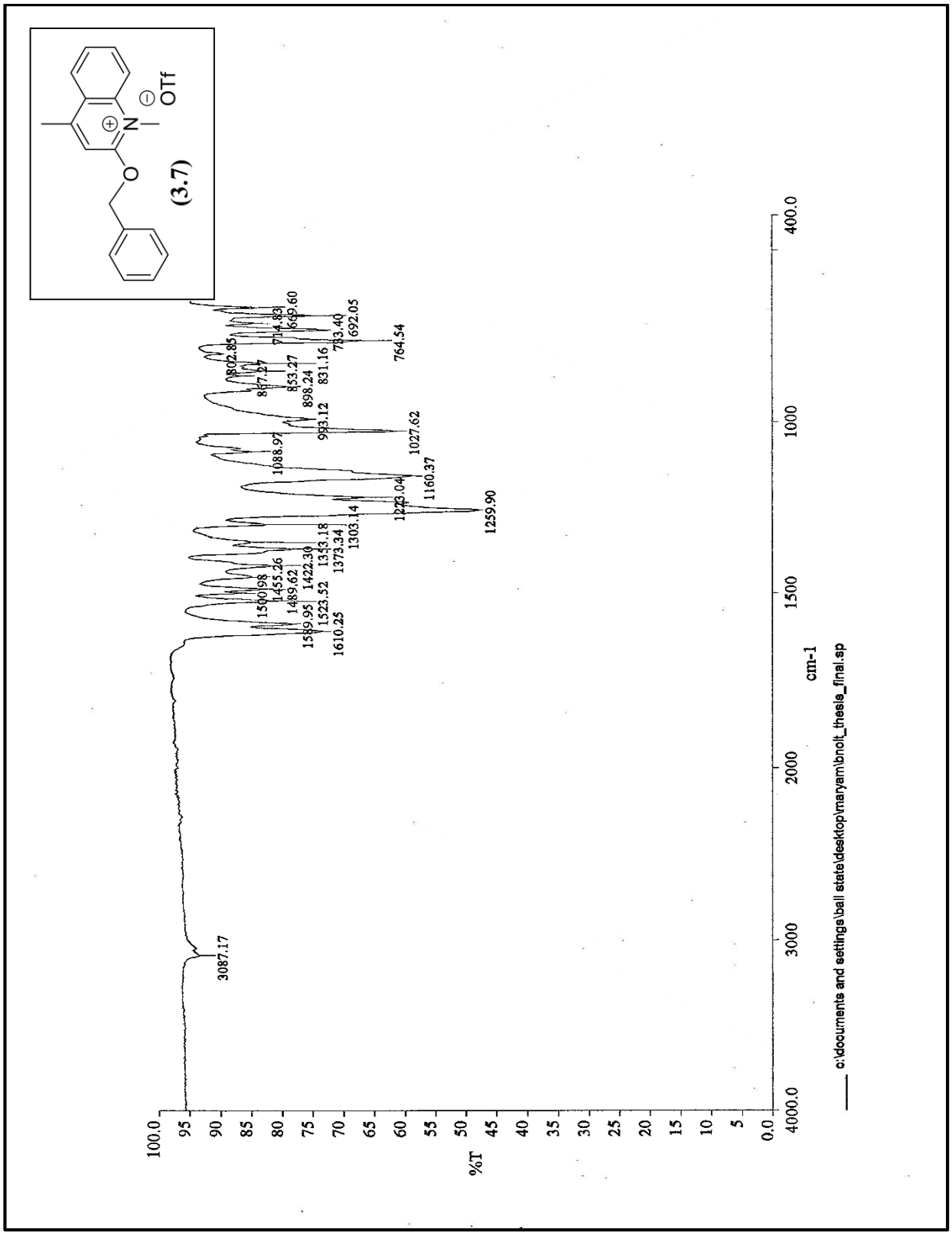
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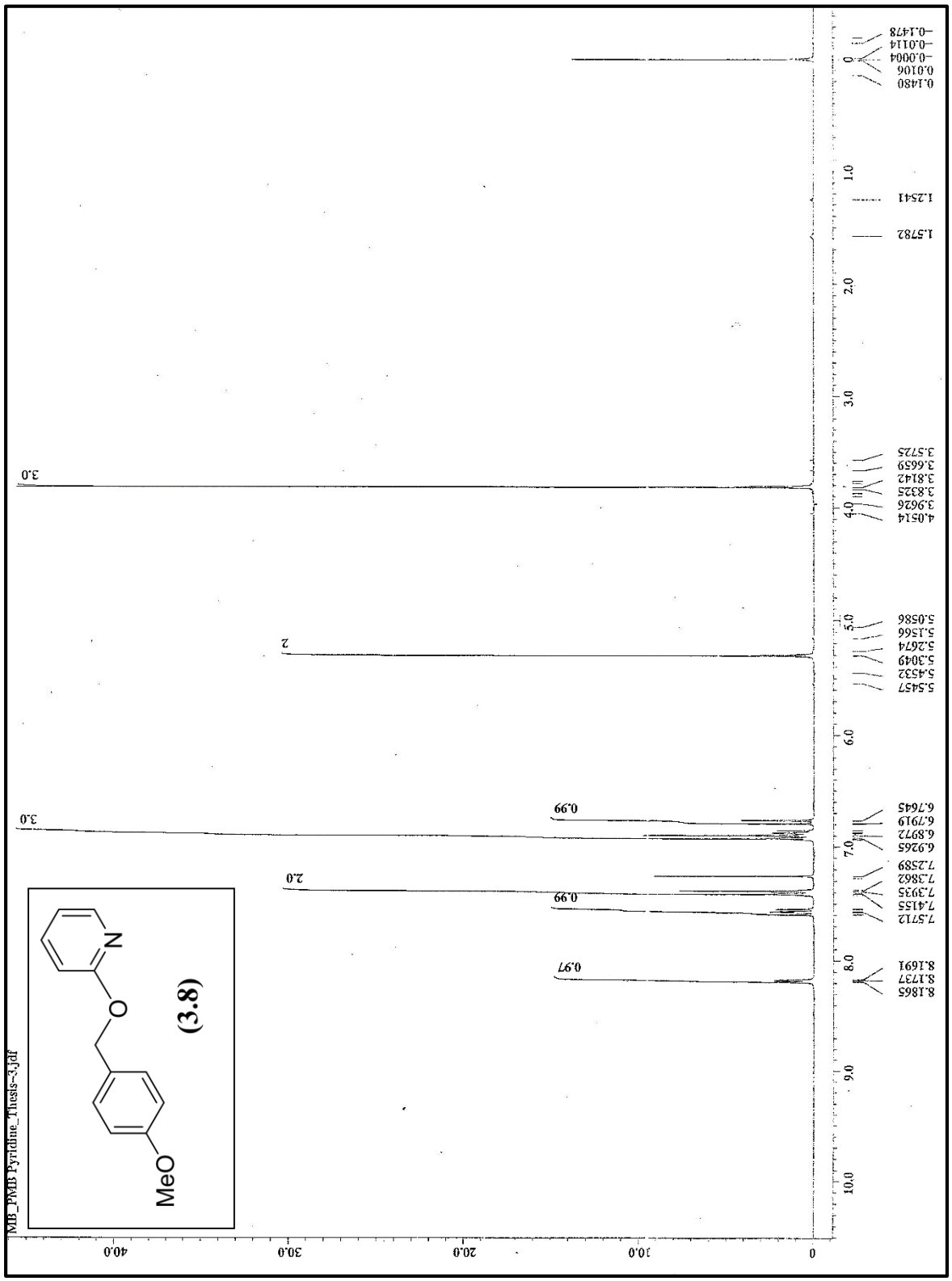
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1.2541
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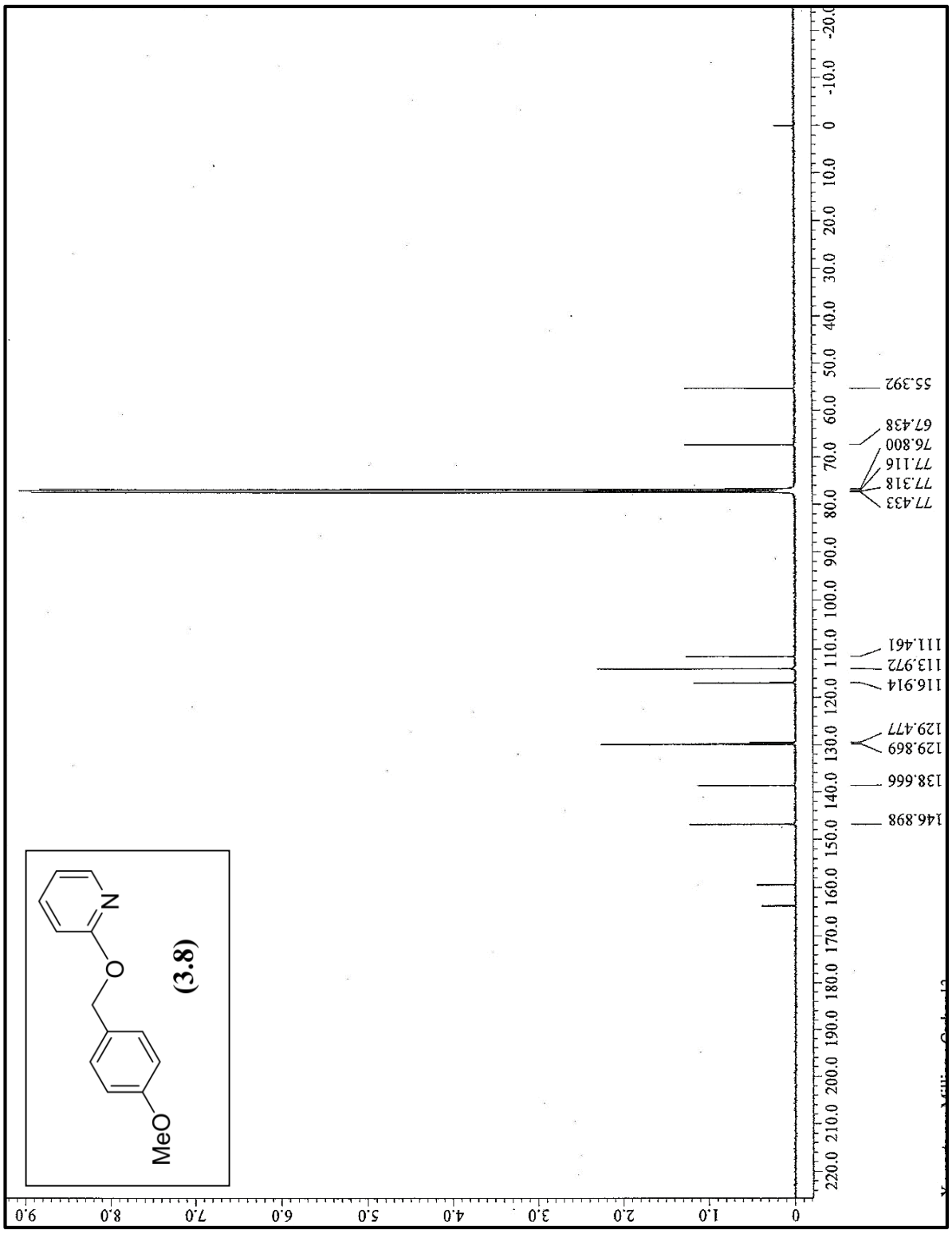
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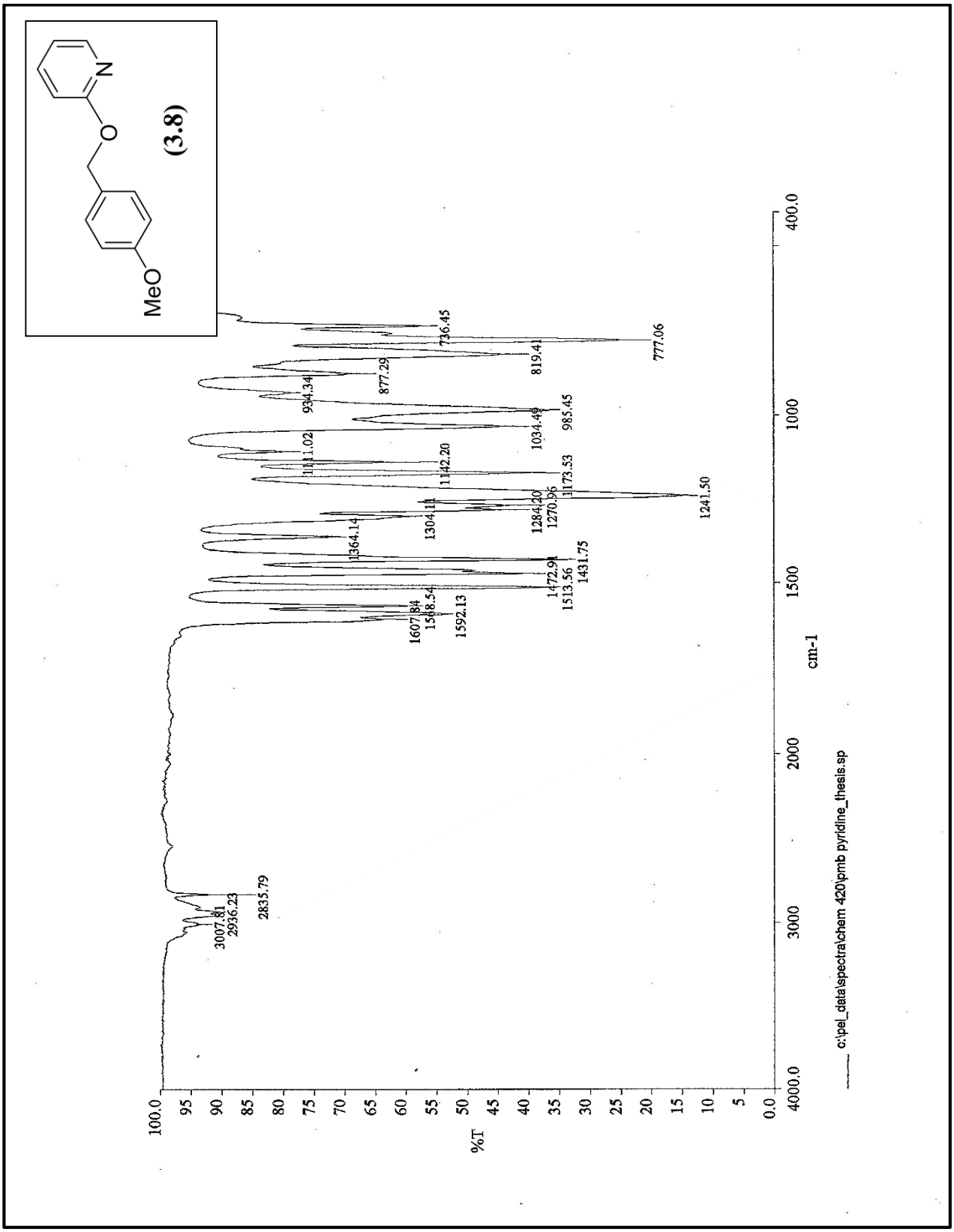
67.438
55.392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1000
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